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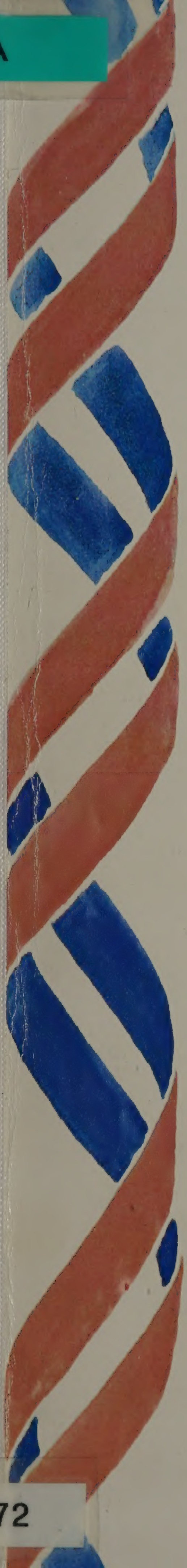

BIOTECHNOLOGY IN CHINA

Report on a Biotechnology fact-finding mission to China

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Biotechnology - China

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REPORT OF AN OSTEMS MISSION TO THE PEOPLE'S REPUBLIC OF CHINA

1 INTRODUCTION

A fact finding mission on biotechnology was undertaken to the People's Republic of China during the period 18th to 28th March 1996 under the auspices of the UK Government's Department of Trade and Industry (DTI) Overseas Science and Technology Expert Mission Scheme (OSTEMS).

The mission was organised on behalf of DTI-OSTEMS by the UK BioIndustry Association (BIA)

The objectives of the mission covered the subject areas of:

i) State of Biotechnology activity in China.

ii) Status of Biotechnology markets in China with special reference to sources of funds available to facilitate purchases of products/technology from UK.

iii) Current status and outlook for Intellectual Property Protection in China to safeguard UK interests in commercial activity.

and the questions of importance to the mission and to British industry, namely

i) What is the range, depth, concentration and location of Chinese Biotechnology -especially given China's stated aim to achieve parity with the developed West in Biotechnology by 2005.

ii) Who/what are the drivers for commercialisation of Chinese Biotechnology and what is the relationship between government and private enterprise? Is there a private, non governmental market?

iii) What markets exist for British products/technology and who controls the funds and hence access to these markets?

iv) Are there technology transfer opportunities from China to UK? If so in what fields and how can they be facilitated?

v) What is the likelihood of effective Intellectual Property Protection of transferred technology and technology generated by joint projects?

vi) What are the opportunities for exchange of personnel to facilitate the above.

2.1 EXECUTIVE SUMMARY

China, the most populous country in the World with 1.2 billion people and an expected growth to 1.5 billion by 2000, is going through dramatic economic and technological changes. She has doubled industrial growth in the last 10 years, her average annual economic rate of growth is 9.2% and she aims to achieve parity with the developed West in biotechnology by 2005.

There is every indication that this will be achieved. The science establishment is undergoing rapid change fuelled by competitive grants, overseas collaboration and by the return of young, eager, Western trained scientists who are replacing the traditional gerontocracy in institutes and university departments.

The funding to achieve this will be from an increase of the percentage of GDP from 0.5% to 1.5% associated to support civil research and development. Policy guidelines are set by the State Council and implemented by the State Science and Technology Commission (SSTCC). Several competitive government programmes, each with a different focus, are available allowing greater autonomy and opportunity to universities and research institutes.

The areas of biotechnology receiving special emphasis include transgenic animals and plants, new pharmaceuticals and protein engineering. Particular emphasis is placed on the development of commercial areas in institutes, departments and particularly, great interest is shown in the establishment of research and development linkages with overseas institutions.

Over the years there has been a major outflow of Chinese students, mainly to the West, for advanced training, including biotechnology. Many have not returned but nevertheless they constitute valuable linkages between China and the West. However, China has been able, through generous financial offers and promotion packages to recruit highly qualified and competent young scientists back to China to form the springboard for the expansion of Chinese science, including biotechnology.

At present the biotechnological science practised is of the “me too” nature, following on work done in the West, much of it at the basic (up stream) level with little application of downstream technology transfer. It is likely these aspects will be of a temporary nature but there is some doubt Chinese biotechnology will rival that of the West in terms of innovation, quality and quantity as early as 2005.

Within this rapidly evolving scene there are major opportunities for British biotechnology companies to participate, not only in basic studies but particularly where the UK is also strong, such as in downstream technology. Such opportunities are also recognised by other countries who are pressing forward with industrial involvement with China.

The UK has always been, and still, is very highly regarded in China for its strength in biotechnology, management and technical skills yet it is considered slow in grasping the obvious commercial opportunities.

Hence the time for action is now: coming in second will be too late. In particular, the UK can supply the important needs of management, fund raising and an understanding of quality assurance, safety and regulatory issues. It is important to understand the Chinese way of “doing business” and the importance of the “Greater China” connections in the economy of China. To be successful in China it is deemed necessary to have a local Chinese contact or partner to facilitate progress.

While IPR protection has yet to reach the sophistication of the West, progress is being made and full protection in IPR for foreigners is being promoted. However enforcement is another matter and a continuing issue.

There is an important need for information to be made available in China about science and technology in the UK and of the structure, function and opportunities for British biotechnology in China. This would be best achieved by booklets produced in Chinese or English about each country’s opportunities.

It is important to establish a firm British biotechnology presence in China and Sino-British Biotechnology Centres are proposed for say Beijing, Shanghai and Shenzen as foci for British companies, for Chinese who have returned to China or are about to do so and to act as Chambers of Commerce. Such Centres would provide information and contacts for biotechnology, arranging lectures and seminars by distinguished industrialists and scientists from China and the UK. To this end the British Council and the Scientific Counsellors of the British Embassy would play an important role, but their number would require to be increased. The existing diplomatic personnel do an excellent job but their efforts are limited by being too few on the ground.

There is no doubt that UK commercial biotechnology would be well received in China but strong positive action on the part of both Government and private industry is essential to remove the stigma that “the British react too little and too late”. The repeated message the OSTEMS Mission received is “Now is the time for action”.

NB: In the text, the abbreviation RMB is used for the Chinese currency unit Renminbi. The approximate exchange rate at the time of the Mission was US$1 = 8RMB.

2.2 TEAM MEMBERS

Team Leader and Representative of the BIA:

Lord Soulsby of Swaffham Prior

Academic Team Member:

Dr. Chris Lowe	Director of Biotechnology, Cambridge

Industrial Team Members:

Dr. Brian Adger	Director, Process Research and Development, Chiroscience plc
Dr. Roger R.C. New	Director of Research, Cortecs Ltd
Dr. John DeLamarter	AssociateDirector, Geneva Biomedical Research Institute (GBRI) GlaxoWellcome Research and Development S.A.
Dr. Geraldine Schofield	Head of External and Regulatory Affairs, Unilever Research

2.3 ACKNOWLEDGEMENTS

The OSTEMS mission members wish to thank the following persons for the assistance and advice at the various stages of the planning, execution and reporting of the Mission

Ms Helen Deas	OSTEMS, Head of Section, International Technology Service
Mr Russell Laverick	OSTEMS, Manager DTI
Dr John Warren	OSTEMS, Director DTI
Mr Patrick Tilbury	Independent Consultant on China
Mr Michael James	China Biomedical Group Inc.
Mr Graham Young	Chairman UK - Asia Pacific Advisory Group on China
Sir Leonard Appleyard	H M Ambassador, British Embassy, Beijing
Mr Stephen Brown	British Embassy; Commercial Counsellor; Director of Trade Promotions in China
Mr Peter Wilson	British Embassy; Second Secretary (Commercial)
Mr Martin Davidson	British Embassy; Cultural Counsellor; British Council, Director in China
Dr Bhaskar Chakravarti	British Embassy; First Secretary (Cultural and Scientific) British Council Deputy Director
Mr Martin Bell	British Embassy; Second Secretary
Mr Simon Featherstone	Her British Majesty's Consul General Secretary
Mr David Putnam	First Secretary; Cultural and Education Section British Embassy; South China Office, Shanghai
Cathy Sheng	British Embassy; Cultural and Education Section
Mr Wang Yan	British Embassy; Commercial Section
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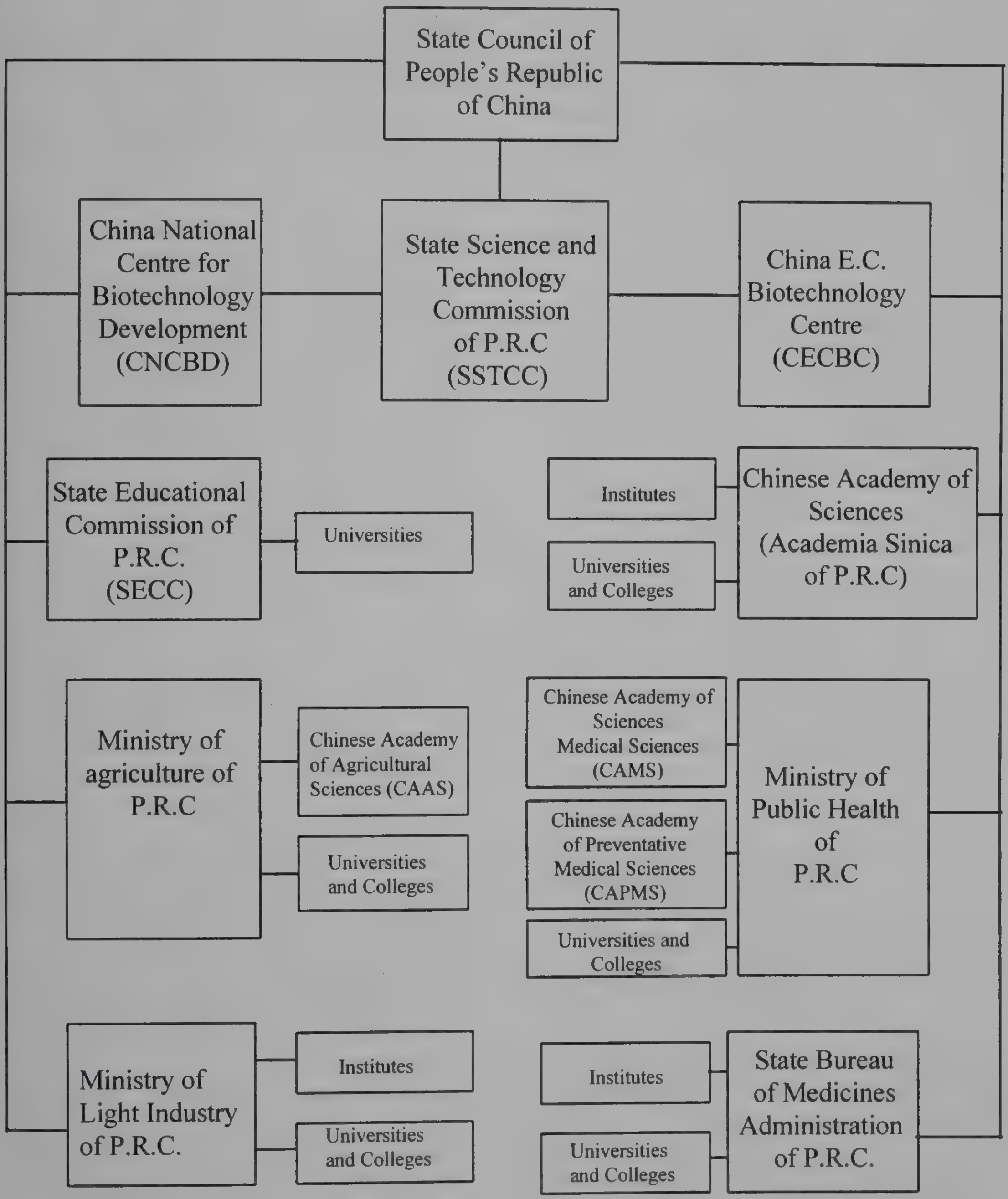
Mr Liu Renqing	First Secretary, Science and Technology Section of Embassy of the People's Republic of China, London
Senior Captain Yin Xianyin	Naval Attaché Embassy of the People's Republic of China, London
Caroline Duncan	BioIndustry Association
Dr John Sime	Chief Executive, BioIndustry Association

In addition members of the mission wish to thank the Chinese colleagues whom they visited for their generous hospitality, their courteous willingness to discuss various issues and to answer many questions. The OSTEMS Mission left China with a sense of having established an understanding and a friendship.

They hope this will be translated into positive collaborative action between the United Kingdom and China.

Table 1:

Chart of relations concerning administration and research relevant to biotechnology research and industry in the People's Republic of China


State Council of People's Republic of China
China National Centre for Biotechnology Development (CNCBD)
State Science and Technology Commission of P.R.C (SSTCC)
China E.C. Biotechnology Centre (CECBC)
State Educational Commission of P.R.C. (SECC)
Universities
Institutes
Universities and Colleges
Chinese Academy of Sciences (Academia Sinica of P.R.C)
Ministry of agriculture of P.R.C
Chinese Academy of Agricultural Sciences (CAAS)
Universities and Colleges
Chinese Academy of Sciences Medical Sciences (CAMS)
Chinese Academy of Preventative Medical Sciences (CAPMS)
Universities and Colleges
Ministry of Public Health of P.R.C
Ministry of Light Industry of P.R.C.
Institutes
Universities and Colleges
Institutes
Universities and Colleges
State Bureau of Medicines Administration of P.R.C.

3 BACKGROUND

The People's Republic of China has a population of 1.2 billion, this being 25% of that of the world and it is projected to increase substantially to 1.5 billion in the coming decade. However, it has a relative dearth of per capita natural resources and for example it possesses only 7-8% of the world's cultivable land. It covers a vast territory yet the development varies greatly from region to region as is reflected by the uneven economic and educational systems in these regions. President Jiang Zemin has stated that the feeding of the population of 1.2 billion must, and can, be resolved by China itself (China Daily, 7 June, 1996).

China is going through dramatic economic change. Following changes initiated in 1956 with the formulation of a 12 year plan for scientific and technological development, a series of major activities, including the High Technology Research and Development Plan (often called the 863 Programme) and the National Natural Science Foundation of China a nation-wide system of competitive external grants, was established. These have resulted in a doubling of the industrial growth in 10 years compared for example with the 50 years necessary for the industrial revolution in Britain to achieve this (1780-1835).

The future plans are to increase, from 0.5% to 1.5%, the fraction of gross domestic product (GDP) devoted to civil research and development and within this to achieve parity with the developed West in biotechnology by 2005, i.e. within 10 years.

Chinese technological development is geographically located mainly along the coastal strip (60%) with a further 30% of development adjacent to that strip. Within these strips there is uneven development and some local zones have been deregulated and are export and foreign investment led.

The eastern seaboard is also where the majority of the population lives and it is estimated that 50-100 million Chinese will move from rural to urban areas in the coming 10 years adding to the existing major increase in consumer goods ownership and demand. Though the basic wage is low, much of it is disposable income as the majority of the basic needs are provided by the State.

Foreign investment is much encouraged in China and examples of various countries inputs are (in billions of US dollars): Hong Kong: 60, Taiwan: 8, USA: 7, United Kingdom 1.3. [The UK is the largest European *investor* in China but is 3rd or 4th in terms of *trade* with her.] The dominance of Pacific Rim countries in inward investment into China points up the role of "Greater China" in investment. This "Greater China" consists of ethnic Chinese round the world and accounts for 8 out of every 10 dollars of foreign investments into China. "Greater China dominates the economies of Malaysia, Indonesia, Vietnam, Thailand and the Philippines and runs the economies of Taiwan, Singapore and Hong Kong.

The economy of "Greater China" is estimated to become the world's 4th largest. But the intrinsic importance of the "Greater China" lies in the method of doing business with other overseas Chinese through a system of trust and connections without contracts or Government oversight - a system based on *Guanxi* or "connections". A feature of the "Greater China" context, in addition to *Guanxi*, is that companies are usually family based, enabling them to move swiftly in response to shifting markets and rules, compared to the much more measured approach taken by large multinational organisations. These latter organisations, increasingly, are appointing ethnic Chinese, China based personnel to help them understand and participate in this method of doing business.

4 GOVERNMENT ROLE IN BIOTECHNOLOGY

A chart of the administration and research relevant to biotechnology research and industry is given in Table 1.

Policy guidelines in science and technology are set by the State Council, the highest body responsible for the running of the country and headed by the Premier.

The formulation and implementation of these guidelines is the responsibility of the State Science of Technology Commission (SSTCC) except in the area of military research which is run independently by the National Defence Science and Technology Commission.

The SSTCC is responsible for the management of the many new competitive funding programmes that include:

The National Natural Science Foundation of China (NNSFC);
The State Key Laboratory Project;
The "Storm the strategic position" or Gongguan Programme;
The "Climbing" or Pandeng Programme;
The "Spark" or "Starfire or Xinghuo" Programme for agricultural research;
The "Torch" Programme for developing high technology zones;
The 863 or the High Technology Research and Development Programme;
The Selection of Research Organisations for loans from the People's Bank of China.

These multiple sources of government funding have given greater autonomy and opportunity to universities and research institutes which now are able, with the institutes of the Chinese Academy of Sciences, to compete in the funding market place and overall research funding is made up of competitive grants, contracts with industry and venture companies set up by the individual institutes.

4.1 SPECIFIC DETAILS OF FUNDING BIOTECHNOLOGY.

Funding of Biotechnology in China derives from six different sources:

1) Government bodies (out of a rolling budget allocated by the State) (SSTCC) at Central, Provincial and Municipal level.

2) Returns from the market after commercialisation of activities

3) Venture capital funds (both internal and foreign) supporting commercialisation activities

4) International Agencies

5) Foreign companies

6) the Chinese military

The various programmes for which the SSTCC has responsibility are listed previously (see 4.). As part of the maintenance of infrastructure, each of these bodies provides overheads for support of its activities, many of which may be biotechnology related, as well as providing some funding for specific projects. However, in order to focus funding more directly into areas considered important for China's economic growth, the Government set up the State Science and Technology Commission (SSTC) in the early eighties to provide extra funds for development in these areas, and to co-ordinate the distribution and exploitation of these funds among the relevant government bodies. The status of the SSTC is at a high level equivalent to that of a Ministry, since its chairman Song Jian sits directly on the State Council. Of the six fields of science identified as requiring attention, one of the highest priorities within the SSTC is biotechnology. In order to operate within this area, a separate organisation was set up within SSTC, the Chinese National Centre for Biotechnology Development (CNCBD) which deals with administration of the money allocated to SSTC for biotechnology projects. This Centre has four main functions:

i) Through an advisory committee, to identify areas of biotechnology to which attention should be given. This evaluation is based on what are considered to be China's requirements for growth, and do not take into account the activities already taking place within Chinese Institutions.

ii) To invite applications for SSTC/CNCBD funds from scientists within China (working within the various Government bodies listed above) on the topics singled out in (i).

iii) To evaluate the projects presented, and select the strongest for support.

iv) To distribute and administer the funding projects selected.

In addition, the CNCBD provides advice on biotechnology development directly to other agencies if requested, but plays no role in administering funds.

The areas of biotechnology supported by the CNCBD are seen as falling into three different categories:

- Agriculture, including transgenic animals and plants, and related cell-culture techniques

- New pharmaceuticals, principally gene and peptide-based therapeutic agents

- Protein engineering, mainly for food purposes

These are supported by two different programmes, one - the biotechnology component of the SSTC's "863" programme, started in 1986 (the seventh five-year plan) when the funding role of the SSTCC was first defined, and the other - the "Key Attack" programme. These two programmes differ in several respects, firstly in that the funding through the 863 programme is considered to be mid to long-term, while that for the "Key Attack" is intended to be for up to five years, after which some material result is expected to be seen from the project. Hopefully, this should lead to funding from another source. Secondly, the 863 programme is much more limited in its scope, projects being restricted to those involving genetic engineering, while the Key Attack programme is broader in outlook; in the agricultural area for example it encompasses work on hybrid strains produced by traditional means. Thirdly, the funding of projects under the 863 programme is 100%, and the budget is stable and assured by the government. The Key Attack programme only partially supports projects, and requires other funding to come from commercialisation etc. In both programmes, however, the funding supplied is intended to cover only research costs - i.e. equipment, reagents etc., and does not include scientists' salaries, welfare costs or building overheads. The annual budget allocated for funding of the biotechnology component of the 863 programme was estimated to be ≥ 0.1billion RMB (~ £80 million). Because of the less stable nature of the Key Attack funding, precise estimates for this programme were not forthcoming, but it was thought that the total scale of activities (taking into account funding from other sources) was no smaller than the 863 programme itself.

Within the CNCBD, a special organisation was set up in 1988, the China United Biotechnology Company (CUBC) to aid in the commercialisation of the results arising from specific research projects. This is essentially a self-funding body, designed to encourage investment in development by other agencies, including foreign companies.

A loan from the Government may be obtained, repayable with interest once revenue is generated from the market. Other funding comes from establishment of the projects as joint ventures with third parties, both inside and outside China. Although the CUBC (technically a "State-owned Enterprise") has arisen from within CNCBD, it is accorded no special status or role by the Government, and has to act in competition with many other organisations set up, either publicly or privately for the same function. Because CUBC was established relatively recently, and is self-funding, its activities do not represent a very large proportion of the total commercialisation activity within China, and unlike CNCBD, it does not have any Government-defined responsibility for overseeing operations in China as a whole. Its independence is further emphasised by the fact that it is not restricted to supporting biotechnology projects which have come out of CNCBD-supported programmes.

An additional activity of the CNCBD is propagating links with foreign countries. This is brought about in the European Union via DGXII, and also through a joint body set up between the EU and CNCBD - the China European Biotechnology Centre (CEBC). This organisation acts as a conduit for information relating to biotechnology in the territories, and is able to help interested parties make contact with each other in specific areas. It is also involved in visits, workshops and other training exercises, although the funding for these activities from the European side is likely to be curtailed shortly. Currently, scholarships amounting to US $20,000 are available to send 10 persons/year to the EU for training. A number of bilateral agreements exist between, for example France, USA and Germany, but there are no formal links in this area with the UK.

4.2 CHINESE ACADEMY OF SCIENCES

Founded in 1958 the CAS enjoys a considerable degree of autonomy. It can obtain funds direct from the State Council for imported equipment and its funds from the Ministry of Finance are protected from any interference by the SSTCC. There are 123 Institutions throughout China, of which 40 are working on research and development in biotechnology with some 1500 scientists employed therein. Of these 38% are senior level, 39% mid-level and 33% junior level.

The CAS states it is entrusted by the government to organise and implement the National key projects of biotechnology which are, (with distribution of personnel to each discipline) Genetic engineering (25.5%), Cell engineering (28.6%), Enzyme engineering (7.2%), Fermentation engineering (21.3%), Biochemical engineering (13.1%) and Protein engineering (4.3%). Additionally, commercialisation and industrialisation of biotechnological achievements are undertaken and academic and scientific exchanges with other countries are arranged. Some laboratories in universities and research institutes are designated as State or National "Key" laboratories. There are some 150 such laboratories, each of which receives a large budget as a start up fund. Every three years they are assessed by an external evaluation organised by the NNSFC. Additional funding is dependent on the evaluation and a laboratory may have the "Key" status withdrawn if it fails to meet required standards on two consecutive evaluations.

CAS income in 1994 was US$325 million, of which 30% was devoted to basic research, 30% to population, resources and the environment and 40% on technology development.

4.3 UNIVERSITIES AND COLLEGES

In a mixed command and demand economy as large as that in the PRC, the organisation of academic establishments such as universities, colleges and research Institutes is often more complex than in western democracies. More than 1000 academic establishments are associated with all the principal ministries including the People's Liberation Army, and the Chinese Academy of Sciences (CAS), the Chinese Academy of Agricultural Sciences (CAAS), the Chinese Academy of Medical Sciences (CAMS) and the Chinese Academy of Preventative Medical Sciences (CAPMS). (These are listed in the document "A guide to major Sci-Tech Institutions of China")
The Universities and Colleges have changed considerably from the previously well established gerontocracy and are now attracting outstanding young men and women, often with experience in the west and with western ideas, to senior positions. Thirty-six of the most prestigious universities come under the jurisdiction of the State Education Commission of China (SECC). It is possible, even probable in due course, that they will be competitive in terms of research and scholarship with the leading academic institutions of the world. Funding is usually channelled through the National Natural Science Foundation of China (NNSFC) for fundamental and basic research and the CNCBD for more strategic and applied research in biotechnology. The funds available for this research appear small, typically 100-150 million RMB (about US$12 to 20 million) per annum for CNCBD, but they only support running costs for consumables and small items of equipment; salaries are paid centrally by the University or College concerned. The concept of 'overheads' appears not to be widely applied, even for externally funded work.

In the case of major science and technology projects, e.g. State key laboratories, pilot plants for industrial scale-up, the State Planning Commission responsible for planning the national economy plays a role and when programmes are necessary to modernise industrial technological development especially with overseas implications, the State Economic and Trade Commission is involved.

Chinese academic links with some overseas countries are strong due to generous scholarship schemes which have taken thousands of Chinese students to countries such as the USA. The fact that many do not return does not appear to concern some officials, others are resigned to it while still others are angry at the haemorrhage of talent overseas. Some academics would mention the fact that there would not be space, facilities or salaries for them if many did return. However, those who stay overseas are an important resource of collaboration and other assistance. They become part of the "Greater China"!

The extent of collaboration is illustrated by the co-authoring of publications with scientists from China and the USA. Of the 5,210 papers per year (averaged over 1985-92) with an author from China, some 600 were co-authored with a scientist from the USA and 364 were co-authored with a scientist from the European Community.

4.4 QUALITY OF FACILITIES IN BIOTECHNOLOGY

The delegation visited a number of Universities (Peking, Qinghua, Beijing, Agricultural, Beijing Union Medical, Fudan, No. 1 Medical), CAS Institutes (Genetics, Microbiology, Biochemistry, Cell Biology, Biotechnology Research Centre) and Institutes of CAAS (Biotechnology Research Centre) and CAMS (Beijing Union) in order to gauge the quantity and quality of research in biotechnology in China. With the exception of one institution, the CAS Shanghai Biotechnology Research Centre, which was requested by the delegation, the other organisations were selected to display the very best of Chinese work in this area. Not surprisingly, the laboratories varied significantly in their age and level of facilities; many had relatively modern equipment such as centrifuges, DNA sequencers, synthesisers, incubators, spectrophotometers and clean air hoods, although in general equipment appeared relatively poorly maintained and serviced. There seemed an element of 'show' in some laboratories, where the staff thought the delegation may be more interested in expensive equipment than the work being undertaken. Overall, the levels of equipment compared to a low to mid-ranking British University, with often the general demeanour of the organisations also being comparable. The infrastructure associated with even the best institutes appeared basic at best and almost non-existent at worst. Whilst everyone recognises that there is little to 'show' for investments in infrastructure, the provision of a high technology facility requires an on-going commitment to both a front-line and back-room capability. Often, we saw examples of expensively purchased equipment being underused or inoperable for want of reagents. An example of this was genetic work where sequencing of loci for candidate disease genes was *not* done because the reagents for the automated DNA sequencer were too expensive. Notwithstanding this, in few of the places we visited could it be said that access to equipment was likely to be a serious impediment to the work being undertaken.

4.5 ACADEMIC RESEARCH IN BIOTECHNOLOGY

Quality of the academic research in biotechnology was more difficult to judge in view of the significantly different environment under which Chinese scientists work. In most cases, it was quite difficult to deduce who was doing the work, or, in some cases, even where the work was being done. With a highly centralised and directed programme such as the '863' programme, it is inevitable that some duplication of research will occur, since the programme specifies particular research topics and there are a very large number of scientists and institutes vying for limited resources. Consequently, of those places visited, most were engaged in research relating to plant, animal or pharmaceutical biotechnology, even where the institute concerned presumably had no obvious brief. For example, the CAS Institute of Microbiology had a very active programme of research into plant virology and genetic engineering, presumably because funding in the more classical fermentation technology had virtually dried up. In one sense, this conveys the message of a very dynamic supply-and-demand economy with research funding following the best proposals and implementers. In practice, however, we suspect that there is still more than a hint of command left in the system. Indeed, this is confirmed in the SSTCC's own brochure on the High Technology '863' Programme which states: "Projects, along with funds, go to the most qualified project implementers through competitive bidding and mandatory system".

The academic research was, by-and-large, "me-too" and following Western research and targets implemented a decade earlier. However, in the context of Chinese material and financial reality this was an entirely reasonable approach. They are effectively creating a new science base *de novo* in areas seriously disrupted during the cultural revolution. However, there do appear to be large gaps in their technological capability which will eventually impede further development of biotechnology in the country. For example, at almost all the University Departments, Institutes and Centres we visited, there was an impressive list of projects involving recombinant DNA technology. The

majority of the '863' Programme encompasses upstream technologies such as plant molecular biology, gene therapy and protein engineering. However, notable by its absence, was any emphasis on the key downstream technologies associated with biochemical engineering, separation science, enzyme technology, cell culture, drug delivery, targeting and formulation. Without these techniques, it is difficult to imagine how developments in the '863' Programme could be brought to the market place to standards accepted in the West. The only organisation we visited which claimed a remit in downstream technologies was the Shanghai Research Centre in Biotechnology. This Institute was the least impressive of all those we visited, with no obvious expertise or facilities on par with the upstream technologies being developed elsewhere. A similar situation was apparent at the Biological Products Institute in Beijing.

The UK could play a decisive role in remedying these deficiencies in Chinese biotechnology, for minimum outlay, by sponsoring studentships or post-doctoral fellowships specifically in the areas of downstream technologies. The UK is traditionally quite strong in biochemical engineering and protein separations and could provide much expertise to assist in areas where the Chinese are obviously weak. Adopting a policy of training Chinese students in these areas, as indeed the Swedish company Pharmacia Biotech does, will also open doors into the burgeoning commercial sector in China. Alongside this proposal, the DTI should consider giving training grants to UK industry for seminars/workshops in the UK or China to establish recognition of British expertise in these key biotechnological growth sectors in the Chinese economy.

It is RECOMMENDED that studentships or post-doctoral fellowships be established to provide training of Chinese scientists in "downstream" biotechnology and it is also RECOMMENDED that DTI should consider the provision of training grants to UK industry to hold seminars in the UK or China.

5 TECHNOLOGY TRANSFER

A key element of the '863' Programme is stated to be the generation of specific products in biotechnology, and whilst there is much talk of the decision making and directing systems, the co-ordinating and administrative systems and the evaluation and monitoring systems, there appears to be little official thought given to how the research is to be converted into products. Technology transfer as it occurs in the West appears to be minimal to non-existent. As far as we could ascertain, technology transfer occurred mainly through key individuals wearing several 'hats' and by a variety of other informal mechanisms.

5.1 THE CHINESE ACADEMIES

All the Chinese academies which support research and development in biotechnology, have established infrastructure organisations such as pilot plants, experimental animal centres and culture collections. They are also engaged in establishing biotechnology enterprises aimed at commercialising and industrialising biotechnological achievements. For example, the Chinese Academy of Sciences claims to have launched 48 biotechnology products and filed 32 patents in the period of the Seventh Five-Year Plan. Furthermore, CAS suggests that nearly a hundred projects to develop new products are "going on quite well". Such products range from virus-resistant transgenic tobacco plants, red algae, all-female carp, diagnostic enzymes and reagent kits, hollow fibre ultrafiltration membranes and the production of 6-aminopenicillanic acid (6-APA) with immobilised penicillin acylase.

An example of an enterprise established under the auspices of CAS is Beijing Kehai Medical Biotech Inc. (BKBI). BKBI is affiliated to Kehai High-Tech Group, which was established 13 years ago and now employs more than 900. The company addresses large potential markets in the biochemistry, biomedical and information technology sectors. The president of Kehai is from CAS and the shares are split 50:50 between CAS and local Government. The ownership of Intellectual Property Rights (IPR) developed by CAS is retained by CAS but can be assigned to Kehai in an exclusive or non-exclusive agreement in exchange for an appropriate level of royalties. All IPR developed within the company laboratories and funded by profits belongs to the company. BKBI has registered assets of 1.2M RMB (US$148,000) from the Kehai Group and last year returned profits of 800,000 RMB (US$100,000). These profits were distributed as follows: 200,000 RMB to repay the investment with interest to the parent group

over 6 years; 100,000 RMB as an administration fee to the parent group; 250,000 RMB for R&D capital, including project development equipment etc.; 150,000 RMB for the welfare fund for company staff for purchasing houses, providing medical insurance and recreation facilities; and 100,000 RMB for staff bonuses. It was not clear from our discussions as to what royalties were payable to CAS, what was the rate of interest on the loan and whether dividends were payable to the shareholders. Furthermore, it is unclear what return either CAS or the local government expect on their investment and how this is calculated. Nevertheless, this route to technology transfer involving both CAS and local Government sponsors does appear to be successful; 40 products in the area of diagnostic reagents have been launched by Kehai Medical Biotech Inc. within 3 years, with a staff of only 12 persons.

Other Chinese Academies also proactively promote technology transfer. For example, the Union Medical and Pharmaceutical Group is an advanced scientific technological enterprise group established jointly by the Chinese Academy of Medical Sciences (CAMS) and the Peking Union Medical College (PUMC) with the Beijing Union Medical and Pharmaceutical General Corporation as the Key enterprise. The scope of operation of this organisation includes the promotion of technical transfer, consultation and training, industrial production and entry into the international market via import and export of high technology products. It is claimed that there are more than 20 products each with an annual turnover of 5M RMB; (US$625,000).

5.2 CHINA NATIONAL CENTRE FOR BIOTECHNOLOGY DEVELOPMENT (CNCBD)

CNCBD was inaugurated on November 3, 1983 under the SSTCC with a major function of promoting and developing biotechnology in China. CNCBD attaches great importance to the commercialisation of biotechnology achievements and the development of bio-industries. The organisation has successfully established several high-tech enterprises: China United Biotechnology Corporation, Shenzhen Kexing Biological Products Corporation, Shenzhen Xinpeng Biotechnology Development Corporation, Sino-Tech Products Corporation, Shenzhen New-Life Pharmaceutical Company Ltd. and Hainan Tianwang International Pharmaceutical Co. Ltd. Some of these companies are joint ventures with China United Biotechnology Corporation (CUBC), an independent state-run enterprise under the direct leadership of the SSTCC of the PRC. CUBC is charged with industrialising the results of scientific research and the development of biotechnology industries in China. So far, CUBC has established six high technology enterprises, four of which are Chinese joint-venture companies (Shenzhen Xinpeng Biotechnology Development Corporation, Zhuhai S.E.Z. Nature, Science and Technology Corporation, Henan Lingbao Zhonglian Fermentation Factory and Qingdao Lizhong Chitin Company) and two of which are overseas joint-venture companies (Shenzhen Kexing Biological Products Corporation, New Biotech Associate). Shenzhen Kexing Biological Products Corporation is a joint venture enterprise of CUBC, Peking's University's Winning Biotech Group and H & Q Asia Pacific, a US investment firm; its main product is Interferon α_{1B} for the Chinese home market. The company plans to export to SE Asia and then go public in the US next year.

5.3 OTHER JOINT VENTURE MECHANISMS

Shanghai Hua-Xin High Biotechnology Inc. is an example of a joint venture company founded by a prominent member of CAS, Professor Xin-Yuan Liu, on 8 February 1993. He holds the position of Chairman of the Board and General Manager and has seen the value of the company increase from 5.7M to 50M RMB over the last 2 years. The company start-up appears to be financed in kind by the Shanghai Institute of Biochemistry and the Shanghai Biotechnology Research Centre and in cash by Shanghai Hua-Lian Pharmaceuticals Co. and Hong Kong Hu-Kang Pharmaceuticals Ltd. and is engaged in the manufacture of recombinant Interleukin-2. The Company has decided to invest more than 100M RMB in expanding at the Shanghai Biotechnology Industrial Park located at the Jinqiao area of Pudong. Construction of a modern cGMP manufacturing facility, advanced research laboratory and state-of the-art quality control department is likely to contribute to raising the output of the corporation to 100M RMB per annum within the next few years.

6 CONCLUSIONS

Key groups in the academic sector are housed in recently refurbished, well equipped laboratories and contain bright, enthusiastic young scientists attracted back from Western laboratories. Government policies enshrined in the 863 Programme appeared to result in undue emphasis on upstream recombinant DNA research and little or no support for the key downstream technologies which would make this genetic research a commercial reality. There is noticeable duplication of some research themes which is accentuated by the competitive bidding/mandatory system. Technology transfer appears to be largely *ad hoc* and contingent upon influential product champions in key academic and governmental organisations, although an influx of overseas investment, especially in the special economic zones, is creating a number of quasi-governmental/private joint venture companies. However, the technology base of many of these organisations currently falls far short of equivalent western standards.

Nevertheless, all of the evidence points to an extremely rapid rate of growth in Chinese biotechnology possibily to place China on par with the western economies within 15 years.

The UK could contribute to this explosive growth by providing access to key technologies required for the exploitation of biotechnology. This is particularly true for the less glamorous downstream technologies and industrial know-how which are absolutely essential for the purification, formulation and commercialisation of products and whose impact would far outweigh the cost, especially in areas of obvious deficiency in China such as blood fractionation, biochemical engineering and sophisticated separation technology. The UK cannot afford to miss opportunities presented by a mass market of 1.5 billion people by the year 2000.

7 REGULATION

7.1 BIOSAFETY

The attached appendix (Appendix III) is the only regulation which exists for safety in genetic engineering. Generally, it is similar in approach to the EU Regulations and US NIH Guidelines. This regulatory Order was drawn up by a National Committee, chaired by the Vice Chairman of the State Science and Technology Commission, currently Madame Zhu Lilan, who is also a member of the High-Technology Programme Coordinating and Directing Panel of the State Council. The Committee also comprises representatives of the Ministries of Public Health and Agriculture and the President of the Chinese Academy of Sciences. The document was drawn up by a technical arm of the Committee under the leadership of the Deputy Director of the China National Centre for Biotechnology Development (CNCBD). The intention is for other Ministries to decide on their own safety Guidelines, based on this document. Although there is a published regulatory Order, there is *no* mechanism for enforcement.

Beijing University has a large number of genetically manipulated crops in field trials but it is noted there was no office to which to apply for permission for such studies. However, staff felt this would come in time. They stated that some of their releases particularly involving virus resistance and *Bacillus thuringensis* toxin were conducted along the guidelines suggested by the USDA. Also, they had received a visit from an EC delegation (including Dr. Roger Hull from the John Innes Institute, Norwich, and Dr. Rudolf Caspar from Braunschweig) reviewing their release and monitoring procedures. This first biosafety meeting took place in Aug/Sept 1993.

At Beijing, and elsewhere, they were sensitive to the interest taken in releases of GMOs by members of the international community. Their transgenic tobacco, resistant to TMV, has been 6 years in the field. From each of the six generations, from 12 different climatic regions, 150 plants have been checked for stability of the construct (91%) and, for major biochemical components. Different climatic conditions appear to have influenced the expression of the 35S promoter.

Recombinant bacteria, which are antibiotic resistant, are being used in nitrogen fixation releases. It was reported that a study by a British group which examined procedures in the three laboratories engaged in this work concluded that the releases were being done in as careful a manner as possible.

Some institutes appear to use the NIH guidelines for laboratory safety (e.g. Fudan).

7.2 PHARMACEUTICALS

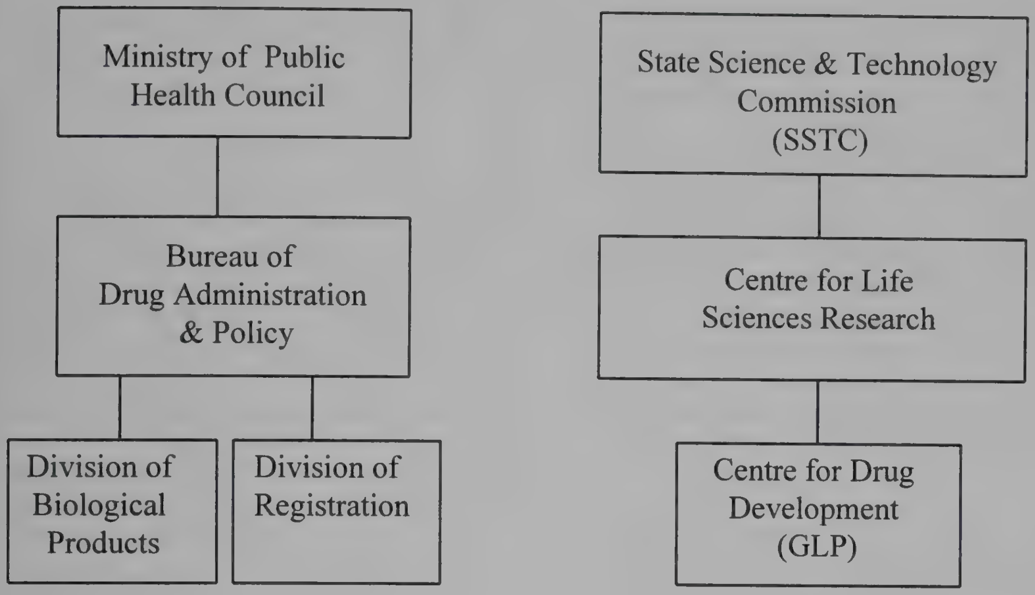
Regarding pharmaceutical products, the Ministry of Public Health was asked if there were differences between approvals for traditional and gene technology products. The response was that 'chemical' pharmaceuticals exported to China are exempt from clinical trials as the authorities will accept data submitted to other regulatory authorities. This was not so for gene technology products, however.

The Division of Biological Products within the Bureau of Drug Administration and Policy in the Ministry of Public Health is responsible for procedures after the R&D phase, and also for putting a product onto the market in accordance with the Chinese regulations. It was stated that the Chinese regulations are 'similar to the FDA'. Clinical trials appear to be easier and relatively cheaper than in the West with more rapid progression through Phase I - III, although one Institute (Shanghai Medical School) reported that clinical trials were very expensive and depended on the hospital. The Bureau of Drug Administration and Policy Centre organises clinical trials and issues certification. The results of clinical trials in China may be published, in medical journals.

The Science and Technology Commission has a Centre for Life Sciences Research and within it is the Centre for new Drug Development which is responsible for Good Laboratory Practice.

GMP is being taken more seriously right from the start of a development programme, although it is far from institutionalised at the moment. In production management Quality Control and Quality Assurance (QA) systems are weak. QA is not widespread.

Table 2. Relationships concerning biosafety and regulation


Ministry of Public Health Council
Bureau of Drug Administration & Policy
Division of Biological Products
Division of Registration
State Science & Technology Commission (SSTC)
Centre for Life Sciences Research
Centre for Drug Development (GLP)

8 INTELLECTUAL PROPERTY RIGHTS (IPR)

The concept of IPR is not a familiar one to the Chinese. The U.S. Government has had long running discussions with the Chinese Government to encourage them to develop effective IPR regulations.

On March 17th, 1992 a Sino-US Agreement on the protection of IPR was reached. On 26th Feb, 1995 the U.S. and China reached an agreement on the protection of intellectual property rights in China. The agreement contained a number of commitments by the Chinese Government including taking immediate steps against piracy in China and making long-term changes to ensure effective enforcement of IPR, thus giving U.S. rights-holders enhanced access to the Chinese market. However, the agreements are not retroactive.

Li Guoguang, Vice-President of the Supreme People's Court is reported as stating that Chinese Courts continue to give full protection to Intellectual Property Rights for both Chinese and foreign IPR owners (China Daily, 6 June, 1996).

Enforcement of the regulations is likely to be a continuing issue as it is a large country and willingness to enforce may be variable. However, efforts are being made to give the issue more attention. In the meantime care should be taken with transferring new technologies with sensitive intellectual property (particularly if the rights are not U.S. patented). Assistance to the enforcement agency has been promised by the EU.

The 32nd International Chamber Commerce Congress is to be held in Shanghai in April 1997 and may be valuable to any Company contemplating doing business in China.

At Beijing University they are using the Monsanto genetically engineered system for cotton for protection against the cotton boll weevil. If Monsanto, who hold all the patents on this, chose to enforce their IPR, the Chinese would have no system to recover royalties. There are no seed companies, all seed producers are owned by the Government and, as such, there would be little income from farmers. However, we were told that any work covered by an International Patent would *not* be developed further.

In collaborative projects between universities and technology transfer companies which are, in the main, also state owned, it was not always clear who owned the IPR. In some cases the university took out a Chinese patent and in some cases this was pursued by the development company. In Beijing, the University was clear that IPR stayed with them.

At Beijing Kehai Medical Biotechnology Company which is 50% Chinese Academy of Science and 50% local Government owned, it was stated that if the Company developed a scientific invention the IPR would be owned by the Company, whereas if the Academy further developed the invention the IPR remains with the Academy. Also, that the IPR can be exclusive or non-exclusive depending on the application. We were also told that multi-national Companies do not pay enough attention to patenting in China.

Particularly with the accession of China to the World Trade Organisation (WTO), there is a mandate from the EU Member States to negotiate IPR agreements. There is a real desire to frame a law, so as to become a serious world competitor, but there is not complete follow through at the moment.

The whole concept of a contract in China is different to that prevailing in the West. Increasing international partnerships are creating an understanding, and changes in the law, but it is a slow process.

It is important for ensuring IPR protection that any new technology to be used in China is patented, and that the patent is also registered in China. It seems that if a patent is published in the West, the product or process can still be patented in China, and will take approximately 18 months.

9 OPPORTUNITIES FOR THE UK IN BIOTECHNOLOGY IN CHINA

With a population of 1.2 billion, set to increase to 1.5 billion over the next 10 years, there are undoubtedly massive commercial opportunities in China.

As stated previously, China has seen dramatic economic growth in the last 10 years, managing to double GDP in that period. Historically, the UK has always been an important capital investor in China, and today we retain a leading position among our EU partners (US$1.3 billion, compared with Germany US$0.8 billion as closest competitor). Despite this, the UK is well behind Germany, and even France and Italy, in trade terms. Last year we sold £824 million in exports to China but imported (mainly commodity) goods worth £1.6 billion. The UK is also the largest single transferer of technology to China. Part of the reason for our relatively poor trading position is political, especially with respect to Hong Kong. There is no question, however, that the Chinese do wish to co-operate and collaborate more with the UK. The political situation is improving, partly due to the intervention of Deputy Prime Minister, Mr. Michael Heseltine who seems to be well regarded in China and, for the first time, reciprocal senior minister level visits are taking place.

During the OSTEMS visit, we were left in little doubt, that in the top institutions, some Chinese scientists are world class and are technically advanced. However, it must be said that most of the research we heard about is "me-too" i.e. most of it is a carry over from work done in the West by Chinese scientists before returning to China. We heard a great deal about transgenic animals and plants, all aimed ultimately at feeding an increasing population efficiently, but we heard nothing really novel. We also heard a lot about gene therapy, where there may be some novelty and about vaccine production, an area where the UK now has little to offer.

In general, the impression gained was that the Chinese do have a good research capability and they are well equipped; indeed many of their top scientists have been trained in the West. What they lack, and where there are opportunities for the UK as a consequence, is management experience, funding, ability to scale-up, and an understanding of Quality Assurance, safety and regulatory issues. In typical joint ventures, the Chinese are looking to their partners to supply these, with themselves providing land and labour. UK companies wishing to do so will have the opportunity to participate in what will surely become the world's largest market in the technology areas mentioned.

There is one area which seemed to us totally unexploited and that is the incredible biodiversity in China, much of which is unique. At the Chinese Academy of Sciences, Institute of Microbiology in Beijing, our host,

Professor Guang-Zhen Ming, informed us that they had over 10,000 microbial strains in their culture collection. The emphasis, however, seems to be on transgenic plants and there is really very little microbiology going on. Even in these days where the emphasis in the West is on rational drug design, a high proportion of drugs on the market, and being developed, derive from leads found in nature. Companies with access to high throughput screening capability should certainly be interested in looking for activity among the metabolites from such a culture collection.

There is little doubt that if British biotechnology companies want to 'get in on the act', they need to do it now; coming second to the table will be too late. In order to be commercially successful, companies will need to find a reliable Chinese partner with the clout to protect IPR. They will need to take a long term view, build a production facility to Western standards, be prepared to invest a lot of executive time and energy and to be patient and put up with frustrations of handling Chinese bureaucracy and culture.

The best way to identify specific opportunities will be to visit China and talk to the relevant people offering help, advice, market research and consultancy services.

If it is RECOMMENDED that British biotechnology companies wishing to enter the Chinese scene should do it without delay.

On our return from China, a letter from Professor George Guo-Quiang Chen, of the Department of Biological Sciences and Biotechnology, in Tsinghua University, Beijing, said it all:

"Novo Nordisk (Norway) invested $200 million in Tianjin to build a modern enzyme plant; Merck (US) is about to finish a large vaccine factory in Shenzhen;Ciba (Switzerland) has a large pharmaceutical plant in Shanghai. However, British biotechnology companies are too slow".

10 WHY IS THE UK NOT DELIVERING? WHAT CAN BE DONE TO IMPROVE UK PERFORMANCE?

Throughout the mission we were told of many investments by other Governments in Chinese biotechnology and science, the UK Government being perceived as one of the lower investors. While low investment can be seen as a major obstacle to collaboration, inappropriate investment can be just as futile. Some of the investments made by other Governments were not as useful as they might appear at a distance. An example is the "Sino-Danish Biomedical Postgraduate Training Centre" located in the former Vaccine and Serum Institute in Beijing. The Centre comprises a modern building with conference rooms, lecture theatre, guest living quarters, and laboratory classrooms all fully equipped and strikingly clean. While the lecture hall was in use and did appear to serve a useful function, the same could not be said of the superbly equipped laboratories. These appeared to be rarely used. In fact we gleaned that the laboratories were only used a few weeks per year. The provision of a modern facility to transfer state-of-the-art information and practices is, in principle, a laudable idea that should have served a noble purpose. However, this example - along with several others - only met one of the criteria for success in China. Establishing a high profile venture that allows the Chinese to participate in a significant fashion, while clearly identifying the overseas partners, is one such measure of success. The failure was due to a lesson that the Mission learned about Chinese biotechnology. By repeated example, during our visit, we learned that the hard currency necessary for instrument maintenance, and for reagents made in the West, is *not* available.

An obvious mechanism to encourage biotechnology and collaborations with the sponsoring country is for that country to provide instruments with which to do the work. However, the lack of maintenance and reagents was the apparent downfall of several high profile projects that we visited. The investment by the World Bank, as well as by the Rockefeller Foundation, in equipment appeared to bring little benefit for these very reasons. Most of the equipment purchased by these grants seemed not to function in its intended role. In China, to benefit from the acquisition of modern instruments, there needs to be a continuing provision for reagents and maintenance. While providing reagents is an open-ended and probably untenable proposition, the provision of maintenance might be considered. However, even providing maintenance is costly and difficult to organise. The training of Chinese

technicians could no doubt be undertaken. Keeping talented individuals in these jobs, however, may be difficult - they may emigrate to higher wage countries. Moreover, providing the spare parts required to maintain the instruments is likely to be highly costly, making the proposal uncertain at best. Thus attempting to provide state of the art instruments, or attempting to maintain them, to encourage a British collaboration with China on biotechnology is unlikely to succeed.

For a number of years now, the Chinese have been sending their students abroad to educate them in the latest Western technology and approaches. From the Chinese point of view these schemes have had significant successes and failures. The successes are the senior scientists (including a biotech company vice president) who have been trained abroad and returned to China to take up their new positions. The widely accepted failure is the very low return rate of Western educated scientists. We were not able to determine the exact overall return rate, however, the percentage of returning scientists is likely to be in the single digits. While some Chinese scientists expressed a resigned acceptance of this fact, others were vocally angry with the loss of talent that they had trained in the first instance. We gleaned that both the formative age of most students and the possibility, in some countries, for staying on encouraged the low return rate. For both its science and English language training, the United States is widely seen as a priority destination. However, the lack of a stricter policy by the United States regarding the return to China of students having completed their training was a clear negative point to the senior Chinese scientists we interviewed. In this regard Britain has a clear advantage in requiring visiting students to return to their home country. This adds to the value of high quality education (and language training) provided in the UK.

Another promising venture that did not yield the expected results was the European Union's *Chinese Communities Biotechnology Centre* (CECB) co-ordinated on the European side by Mr. Luc Vandebon, First Counsellor for Science & Technology, Delegation of the European Union Commission in Beijing. First set up in 1987, the Centre concentrated during the early 1990's on environmental, biotechnological, medical, and agricultural issues. Mr. Vandebon told our Mission that the initial idea was well received by the Chinese and resulted in some of the best personal contacts available in Chinese biotechnology. However, the value of the CEBC has fallen dramatically with the new European Framework Programmes. According to Mr. Vandebon, the intervention of excessive bureaucracy and reduced budgets have significantly reduced the effectiveness of the Centre. The new rules require two European countries (preferably one being a Mediterranean rim country) and two Asian countries (although China is now considered large enough to count as two) to submit a joint proposal. This has to be done to such short deadlines that the co-ordination needed within and outside China is rarely achieved. The complexity and difficulty in meeting the requirements combined with the significant reduction in available funds (previously about 14 -15 million ECU now 5 million ECU), have made the programme much less interesting to the Chinese. Nonetheless, the original model of this venture is certainly an interesting one to explore and hopefully re-create in a form that would support expansion of UK interests.

10.1 WHAT CAN BE DONE TO PROMOTE UK BIOTECHNOLOGY INTERESTS IN CHINA?

An important approach to a solution to the problem of ensuring the best industrial and scientific collaboration would be the establishment of *Sino-British Biotechnology Centres*. These should be set up with a physical site (offices, meeting rooms, lecture theatre) where a brass plaque could announce the importance of the venture. The purpose of the Centres (perhaps one each in Beijing, Shanghai and Shenzhen) would be multifaceted.

First the Centre should provide information on opportunities available in the UK for both commercial and academic ventures. On the commercial side, the Centres could provide contacts for both small and large companies to find the right individual for the project in mind. Thus the Centre would be expected to have both the names of prominent Chinese and British individuals in the field as well as detailed descriptions of the current work on going in the area. Similarly, the Centre would encourage visits from UK business leaders in the biotechnology field as an imperative stop on a visit to China. In parallel, establishments

should bring prominent Chinese to the Centres and to UK. In the best circumstances the Centres would be very proactive in ensuring the visit of prominent UK industrialists and scientists. This could be done by inviting distinguished individuals to give lectures. The lobbying of prominent British industrialists during visits to invest in China should be another function of the Centres' staff. Also, the Centres should organise and finance symposia and meetings on biotechnology in its various forms with participation from both UK and Chinese experts.

The Centres could also serve the role of a Chamber of Commerce for British businesses in the area, providing information on topics of interest to the business community and assisting expatriates in settling into a foreign environment. As an example, the American Chamber of Commerce in Shanghai produces an outstanding handbook - "A guide to living and doing business in Shanghai".

It is RECOMMENDED that Sino-British biotechnology Centres be established in China.

To ensure a long term continuance of Sino- British collaboration on biotechnology at relatively low cost, the academic sector must be involved. The Centres should, perhaps, be recipients of UK government grants for exchange visits to the UK for distinguished established scientists and other professionals. Chinese nationals of this background were seen as the most likely to return to China. A UK experience is likely to translate into a 'UK first', approach to goods and practices in the field. In addition, the Centres should be the recipients of extra UK government funded studentships in biotechnology for distribution by the Centre. This second group will provide the longer term bridge for Sino-British collaborations. Selection of students for these special scholarships should be by interview held within the Centres. Information about both of these types of grants should be available in the Centres and this should be widely advertised in China and the UK. Since training is a highly cost-effective mechanism for encouraging further interactions with the sponsoring country, these grants should be well funded.

The proposal for special Sino-British Biotechnology Centres should not be lightly undertaken. There would be a significant cost to fund the offices, individuals and grants needed to make them a reality. However, compared to other countries' investments in alternative forms of collaboration (e.g. training centres or equipment), they represent a cost effective means of continuous and high level collaboration. With exchange grants for industrialists and academics, the Centres should be able to deliver short and long term collaborations between Britain and China in biotechnology. The Centres would then become a true foundation for continuing collaboration in biotechnology. This field is perceived, not only by the Chinese but by many other governments, from Japan to the United States, as a critical corner stone of future high technology. To *not* fund the exploitation of the excellent science (already paid for in the United Kingdom) in a major market such as China is to cede the future of Chinese biotechnology (and perhaps a great deal of the field itself) to others.

Repeatedly during the OSTEMS visit it was stated that Chinese scientists and administrators were unaware of the structure and funding of scientific establishments in the United Kingdom and the opportunities for collaboration, visits and training. Similarly, and empirically, there is a marked lack of knowledge about China, and its potential for investment and trade, in the United Kingdom.

An answer to both these situations is a greater effort to educate the scientific and industrial community with regular information releases from the United Kingdom, the DTI and other Government bodies. In China, it is particularly important to strengthen the Scientific Counsellor personnel in the British Embassy and Consular offices elsewhere. The existing consular officers do an excellent job but their number and relevant knowledge can not begin to compare with that fielded by competing nations, such as the USA.

It is RECOMMENDED that an information booklet, in English and Chinese, be drawn up on the structure and funding of scientific establishments in the UK and on opportunities for collaboration, visits and training in biotechnology.

It is also RECOMMENDED that a similar information booklet, in English, be drawn up on the structure, funding and opportunities in China for United Kingdom biotechnology companies.

It is further RECOMMENDED that additional Consular officers with relevant skills be appointed to strengthen the Scientific Counsellor services in the British Embassy and Consular Offices in China.

11 SUMMARY OF RECOMMENDATIONS

It is RECOMMENDED that:

- Scholarships or post-doctoral fellowships be established to provide training of Chinese scientists in "downstream" biotechnology.
  (para 4.5).

- The Department of Trade and Industry should consider the provision of training grant funds to UK industry to hold seminars in the UK or China aimed at establishing British expertise in key biotechnology growth sectors in the Chinese economy.
  (para 4.5).

- British Biotechnology Companies wishing to enter the Chinese market should do it without delay.
  (para 9.0).

- Sino-British Biotechnology Centres should be established in China to provide information on opportunities in China, commercial contacts and to serve as a focus for lectures and seminars by distinguished industrialists and scientists from China and the United Kingdom.
  (para 10.1).

- An information booklet, in English and Chinese, should be drawn up on the structure and funding of scientific establishments in the UK and on the opportunities for collaboration visits and training in biotechnology
  (para 10.1)

- An information booklet, in English should be drawn up on the structure, funding and opportunities in China for United Kingdom biotechnology companies.
  (para 10.1).

- Additional Consular officers with relevant skills should be appointed to strengthen the Scientific Counsellor services in the British Embassy and Consular Offices in China.
  (para 10.1).

12 GLOSSARY OF ABBREVIATIONS

SSTCC - State Science and Technology Commission of PRC.

CNCBD - China National Centre for Biotechnology Development

CUBC - China United Biotechnology Company

CEBC - China EC Biotechnology Centre

CAS - Chinese Academy of Sciences (Academia Sinica of PRC)

CAAS - Chinese Academy of Agricultural Sciences

CAMS - Chinese Academy of Medical Sciences

CAPMS - Chinese Academy of Preventive Medical Sciences

NNSFC - National Natural Science Foundation of China

SECC - State Education Commission of China

BKBI - Beijing Kehai Medical Biotech Ltd

IPR - Intellectual Property Rights

PUMC - Peking Union Medical College

Appendix I

Summary of aims and progress of Biotechnology programmes in the Peoples Republic of China.

The following are brief accounts, thumb-nail sketches, of some of the programmes in biotechnology grouped under topic areas. Since the overall programme on biotechnology in China is vastly wider than the OSTEMS mission was able to cover, it is certain that some major undertakings have not been included as the Mission was not informed about them as it visited only a small number of institutes. Nevertheless, while avoiding undue brevity, the following account probably provides a guide to the proportionate effort directed to various areas.

Agriculture

The State Science and Technology Commission (SSTCC) has set as targets for the end of the century (through the 863 High Tech programme):-

- New recombinations of hybrid rice with 20% increase per unit area yield
- enhanced nitrogen fixation of maize, soya bean and vegetables to reduce by a quarter to a third the need for chemical fertilisers
- breeding new varieties of wheat with an average increase in protein composition by 5%
- development of new disease/insect resistant high protein vegetable species
- development of high protein/drought salinity tolerant herbage strains
- cultivation of disease/cold resistant new fish feeds with a growth rate increase of 20 -100%
- raising of new breeds of fast growing lean meat pig, disease resistant poultry and other livestock
- improvement in the reproductive performance of dairy cattle

These various aims are seen as part of a new industry of agro-biotechnology which is promoted by the China National Centre for Biotechnology Development (CNCBD).

Plant Biotechnology

Within the Chinese Academy of Sciences there are basic studies of plant gene structure, function, expression and regulation, signal transduction of plant differentiation of and development, molecular mechanisms of plant pest and disease resistance and plant genetic engineering.

In view of the heavy cotton losses in 1992 (6 billion RMB loss) much effort is directed to the induction of insect resistance to cotton boll weevil. The insect specific neurotoxin from scorpion venom has been synthesized in its non-toxic form for mammals and will be used for insect control trials. An example of work on plant nutritional improvement was the increased sulphur amino acid control of alfalfa to improve sheep wool production and of induction of resistance of potatoes to *Pseudomonas* with the Cercropin B gene.

Rice and soyabean mapping studies were undertaken to achieve a better understanding of photosynthesis and insect resistance.

The use of plants for the production of animal biologicals is illustrated by the introduction of a virus genome into potatoes to protect humans against the virus. Antibody has been produced in mice fed potatoes containing a virus gene. Further studies involve expression of the gene in potatoes and cucumbers.

Post-harvest pathology of fruits and cereals, with reference to the ripening and storage of fruits such as tomato and kiwi fruit, is being pursued.

Extensive basic studies of plant genetics, the development of bacterial, virus and insect resistance using synthetic polypeptides, the improvement of protein and other nutritional content of a wide range of crops and the generation of new crop products are in progress in several laboratories of the Chinese Academy of Agricultural Sciences.

Animal Biotechnology

Less attention appears to be being paid to farm animal biotechnology. Nevertheless, studies were reported on transgenic fish (carp), pigs and rabbits (growth promotion). The use of transgenic sheep for the expression of pharmaceutical proteins in milk has received attention but as yet there does not appear to be any commercial production of this.

Elsewhere (e.g. Bilong Institute for Transgenic Animals in Beijing) there are ambitious plans to develop transgenic animals (and plants) as bioreactors to produce biologically active molecules, to establish transgenic animal models for the study of disease or for pharmaceutical evaluation of drugs. A novel aim is to introduce genes for traditional Chinese medicine such as tiger bone, antelope horn and rhinoceros horn, into domestic livestock and thereby protect the rare species at present under threat of extinction!

Medicinal Products

Several institutes and laboratories undertake research leading to diagnostic reagents and vaccines. An important infection in China is Hepatitis B and diagnostic kits and vaccines (plasma derived and recombinant vaccine) dominate the vaccine production. The market is vast. Other vaccines include Japanese encephalitis, yellow fever, measles, meningococcal and BCG for humans. Blood products include human albumin, anti-hepatitis B immunoglobulin, human blood coagulation factor IX. A recombinant interleukin 2 and gamma interferon are now on the market for cancer therapy. Epidermal growth factor for burns is now marketed and gene therapy for haemophilia is being developed. The naked DNA vaccination approach is under close study at the National Vaccine and Serum Institute, Beijing.

There does not seem to be any major undertaking on animal health products. A vaccine against piglet diarrhoea (agent not determined) was cited. A rabies vaccine using various viral vectors was reported at the Beijing Biological Products Institute.

Basic Biological Studies

A wide range of biotechnological studies are in evidence. Biochemistry and molecular biology dominate many of the studies of the regulation of gene expression in human development and reproduction, development of the neural system and of the human genome studies of the Chinese population (e.g. National Laboratory of Medical Molecular Biology). The structure and function of enzymes and biomembranes are a dominant part of the work in the Shanghai Institute of Biochemistry, of which the State Key Laboratory of Molecular Biology is a part.

Protein chemistry and engineering research across a range of species including the giant panda, is undertaken at the College of Life Sciences of Beijing University.

Basic biological studies are considered increasingly important and are promoted by young Chinese scientists returning from overseas some of whom have been recruited back to China by handsome financial offers of employment and prestigious positions.

Appendix II

Biotechnology Research Institutes and Corporations visited by the OSTEMS group

CHINA UNITED BIOTECHNOLOGY CORPORATION (CUBC)

The CUBC is an independent state-run enterprise established in 1988 to industrialise the scientific developments of the China National Centre for Biotechnology Development (CNCBD) and its high-tech enterprises some of which are joint ventures with CUBC. (see 5.2)

CUBC has many projects under the National Torch Plan. It has provided overseas equipment large and small to various companies and research institutes. It organises overseas scientific exchanges.

It operates under the leadership of the State Science and Technology Commission (SSTCC).

Its International Cooperation Department role is to create and manage CUBC's overseas companies, to export bioproducts, pharmaceuticals, etc, introduce advanced international technology and manage collaborative exchange and establish and manage international collaborative partnership and joint-venture enterprises.

PEKING UNIVERSITY

Professor Chen Zhangliang is Vice President, Peking University and Director, National Laboratory of Protein Engineering and Plant Genetic Engineering. Founded in 1988 it has rapidly developed into the country's largest institution of higher education. Currently there are 73,000 undergraduates, 10,000 postgraduates and 20,000 adult education students enrolled at the University. It now comprises 6 colleges and 29 departments with 85 specialities for undergraduates, 146 specialities for Masters and 97 for Doctoral candidates. The University promotes basic sciences, although, more recently, has paid special attention to the development of applied sciences. The University now hosts 45 research institutes, 52 research centres, 2 national engineering laboratories, 42 key national disciplines and 5 national key laboratories and aims to rank among the world's best universities by the beginning of the next millennium.

College of Life Sciences

The College of Life Sciences of Peking University was inaugurated in November 1993 and comprises 6 departments (Biochemistry and Molecular Biology, Cell Biology and Genetics, Physiology and Biophysics, Plant Molecular and Developmental Biology, Environmental Biology and Ecology and Biotechnology) and several research and development entities (Life Science Centre, Institute of Molecular Biology, Institute of Cell and Molecular Pharmacology, National Laboratory of Bio-Membrane and Membrane Engineering). It has 246 staff, including 43 full professors, 65 associate professors and 125 lecturers, assistant lecturers and other personnel. It was claimed that the College was number one in the country and enjoyed the largest number of grants from the High Technology ('863') programme and the National Science Foundation (NSF) of China, and had two members on the all important CNCBD Grant Committee.

Department of Biotechnology

The main component of the department is the National Laboratory of Protein Engineering and Plant Genetic Engineering, which was established in 1987 with support from the State Commission of Planning, Commission of Science and Technology. It is relatively well equipped with modern instruments including an automatic DNA sequencer, ABI DNU synthesiser, PCR machine and electrophoretic equipment. It appears to be one of the more active centres for molecular biology in China and receives over RMB 1M per annum in grant money, including funds from Rockefeller Foundation, UNIDO and EU.

Pharmaceutical biotechnology and agrobiotechnology are the two main areas of interest, and these sectors both represent the cornerstone technologies of Chinese biotechnology policy.

Agrobiotechnology

There is major concern in Chinese agriculture that there will not be enough food production in the next century to cope with population

growth to 1.5 billion, and exacerbated by development pressures on agricultural land and devastation caused by pathogenic viruses, bacteria and fungi. A particular concern is to increase production of rice, wheat and cotton and to produce transgenic fish, pigs and rabbits. One of the major projects of this group is to clone genes encoding coat proteins of several viruses and transform these genes into plants to obtain virus-resistant transgenic plants. The coat protein genes of tobacco mosaic virus (TMV), cucumber mosaic virus (CMV), potato X virus, potato Y virus and soya bean mosaic virus have been cloned and most of them transformed into transgenic tobacco, potato, pepper and soya bean plants. The group have over 6 years field experience of transgenic plant release and claim to be working to USDA regulations. The transgenic tobacco, PK873, has been field tested in 12 different climatic zones, and over 6 generations, greater than 91% stability has been noted with no apparent change in the quality of the tobacco. Each year 150 plants are tested. The toxin gene *Bacillus thuringiensis* has been cloned into cotton plants to alleviate the effects of the cotton boll weevil and has been field trialed for the last 21/2 years.

Other related projects involve isolating anti-fungal or anti-bacterial proteins from vascular plants or antagonistic bacteria with particular attention paid to screening for proteins which inhibit the growth of *Piricularia oryzae* (rice blast) and *Xanthomonas oryzae* (rice bacterial blight). A number of proteins and peptides have been isolated and shown to have broad spectrum anti-bacterial or anti-fungal activities.

Protein Engineering

The protein engineering group aimed at the over-expression of a number of 'me-too' pharmaceutical targets. A joint project with the Shanghai Biotechnology Centre on the expression of recombinant human insulin in *E.coli* and yeast is at the toxicity, clinical trials and pilot plant stage. The genes coding pro-insulin analogues which contain mini-C peptides of 6 and 2 peptide respectively have been cloned and shown to have radioimmunoassay and clinical activity. A second major project involved cloning and over expressing the thrombolytic human pro-urokinase, is at pilot stage in China and phase 3 clinical trials in the US. Other projects include the expression of calf recombinant chymosin in *E. coli* which is 'nearly' in the pilot plant and temperature mutants of glucose isomerase stable to 40°C.

The Department of Biology has strong interest in the cloning and overexpression of anti-coagulants such as hirudin, thrombolytics such as pro-urokinase and tissue plasminogen activator (EPA) and cytokines such as colony stimulating factor (CSF). It was not clear how all these studies were coordinated or where the pilot facilities were located. It was evident, however, that the laboratories were freshly redecorated and well equipped by international standards.

Studies on protein engineering of metallothionein (MT) and MY0 like proteins have isolated MTα and β domain fragments and shown the relationship between their structure and function by using the techniques of protein engineering. The natural MT gene, α-domain gene and poly-α-domain gene have been separately transformed into tobacco and petunia. The transgenic plants containing MT, α or α_{12} oligomer expressed high resistance to $Cd^{2+,}$ Hg^{2+},and Pb^{2+}. Greenhouse and field trials of these transgenic plants are currently underway. Work is also apparently proceeding on transgenic cyanobacteria which display heavy metal resistance, although no details were given.

Other work is related to the study of spider and plant toxins: for example, the structure of a 33 amino acid residue toxin from the spider *Selencosmia huwena* has been determined by NMR and key residues mutated to increase specificity for insects compared to mammals. The group is currently investigating the use of peptidomimetics as alternatives and has expressed a scorpion toxin gene in bacculovirus in order to create a novel insecticide.

The overall impression gained from the visit to Peking University was that the individuals were quite capable but were involved in research which lacked novelty and was somewhat behind that being conducted in the West.

QUINGA UNIVERSITY

Quinga University is a polytechnic university resembling MIT with strong science departments. The faculty comprised 10 full

professors and 17 associate professors and most had PhD's from overseas, notably from the UK, Germany, US and Japan. The main departments of interest to biotechnology were biophysics, biochemistry, molecular biology and neuro science/cell biology although there is also a rehabilitation centre in Biomedical Engineering. The School of Life Sciences has research funding from the National Science Foundation of China for basic research and from an unspecified industry for work on biodegradable plastics.

CHINESE ACADEMY OF SCIENCES - BIOTECHNOLOGY PROGRAMMES

(see also 4.2)

Funding for the approximately 40 institutes within CAS participating in biotechnology through the seventh 5 year plan was 169 million RMB over 5 years of which 61 million was investment in capital, 22% from the National Key Attack programme, 32% from the High -Tech (863) and 5% form CAS' own Key programme.

Summary of Highlights of Research Activities in which CAS has been involved

Products close to market, or available commercially:

Hepatitis B vaccine - 10% of population are carriers, including several million babies affected per year.
IL2 - *E. coli* expresses 40% of protein as IL-2
Vaccine against diarrhoea in pigs
Interferon (α & γ) - 70% of secreted protein in *E. coli*
Penicillin G - 7,000 tons produced per year, of which 3,000 tons exported.
Converted to 6-amino penicillanic acid using a cloned enzyme expressed in *E. coli.*
Two-step fermentation synthesis of vitamin C (alternative to six-step Reichstein Grunner process)

In Phase II:

- Erythropoeitin

Early development stage:

Monoclonal antibody treatment and diagnosis of Colon Cancer and Encephalitis B.

Chinese Academy of Sciences: Institute of Genetics

The Institute was originally founded in 1959 with 100 employees and now has 465 employees, of which 350 are scientists, with 25 full professors and 80 associate professors. The work of the Institute includes plant breeding, especially of rice, wheat, corn, soya bean and rape seed; the production of bulk microbial enzymes such as α-amylase and proteases; transchromosomal engineering and molecular cytogenetics; human genome diversity; plant biotechnology, especially genome mapping of soybean, and a study of osmoregulatory genes; the molecular mechanism of photoperiodicity in rice; the introduction of virus and insect resistance into cotton and rape seed, and, finally, animal genetics and embryo transfer. However, despite this impressive list of research topics, time was too short to assess the quality of the laboratories. However, the quality of the research could be inferred from the fact that 10-20% of the funding of the Institute came from international sources. For example, Bayer apparently provide US$70,000 per annum, out of a total income of US$1.5M per annum, inclusive of salaries. Much of the foreign currency is used for purchasing instruments and fine chemicals.

Chinese Academy of Sciences: Institute of Microbiology

The Institute of Microbiology was founded in 1958, its predecessors being the Beijing Laboratory of Microbiology and the Institute of Applied Mycology, both of the CAS. It is now a comprehensive research institute with about 430 members of staff, of whom 130 are senior research fellows and 3 are academicians. It has now six departments: Microbial Taxonomy and Culture Collection, Plant Virology, Microbial Ecology, Microbial Metabolism, Microbial Enzymology and Microbial Genetics. The State Key Laboratory of microbial resources and the two open laboratories of the CAS - systematic mycology and lichenology laboratory and plant biotechnology laboratory - were set up in the Institute of Microbiology. In addition there is a pilot plant with necessary equipment for fermentation.

Of the research undertaken 35% is on genetic engineering, 29% on cell technology, 14% on biochemical studies and 14% on enzyme technology. Funds derive from the National Key project, National High-Tech (863), Capital funds for imported equipment and CAS.

The department of microbial taxonomy and culture collection holds 6075 strains of fungi, 1784 strains of bacteria and 1284 strains of actinomyces and was considered to be a particularly rich source of genetic diversity. The department of microbial ecology is in part concerned with biodegradation of environmental pollutants and biochemical treatment of individual waste.

Information was provided by individuals on their own work during the meeting. Two enzymology projects were described, involving immobilised lipase for acting on fatty acid and fatty alcohols in organic phase. Also, the production of dextranase for prevention of caries in children.

Chinese Academy of Sciences: Institute of Biochemistry

The Shanghai Institute of Biochemistry was established in 1958 with a focus on biochemistry and molecular biology with an emphasis on basic research on structure-function relationships of biomacromolecules, molecular genetics and genetic engineering, and biomembranes. The Institute aims to apply practical molecular biology to solve significant problems in agriculture, medicine and industry. The Institute is universally known for its total synthesis of insulin in 1959. Today, the Institute houses 37 research groups, contains 250 scientists, of which 80 are senior i.e. at professor/associate professor level, and a graduate school comprising 150 Ph.D./M.Sc. students.

The principal areas of interest to the biotechnology community are the structure and function of biomolecules, such as insulin and cytokines (Interferon, Interleukins), mammalian and plant viruses, muscle proteins, and anti-sense technology. A key project is the over-expression of Hepatitis B surface antigen for vaccine production. The group is studying gene regulation and transcription and has identified an enhancer and related promoters for expression of the surface antigen; they now use a yeast expression system and are working closely with the Institute of Biological Products. Apparently, pre-S epitopes have been included in the vaccine and direct DNA injection into mice have elicited the formation of a pre-S antibody. Whilst, this route has been shown to be effective in rats, rabbits and chimpanzees, direct injection into mice is new. The purified protein has also been injected into mice to elicit antibody formation. The group have now expressed Hepatitis A surface antigen to produce a protein neutralising antibody, although this study is at laboratory scale only, and attempts are currently being made to express the core and envelope proteins of Hepatitis C. The latter is becoming of increasing concern in China.

Professor Liu Xinyuan of the Institute is a member of the Chinese Academy of Sciences, a member of the New Drug Developing Committee and the president of Shanghai Hua Xin High Biotechnology Inc. He outlined research at the Institute: Expression of cytokines such as Interleukin-2 (IL-2) in *E. coli* resulted in expression rates as high as 80% of the total bacterial protein, and after solubilisation of the inclusion body and purification, a product of purity >90% has been obtained. A typical 10L fermentation will yield 2-3g of purified IL-2. Whilst IL-2 is known to have indications for the treatment of renal cell cancer and malignant melanoma, it was claimed that IL-2 had analgesic properties and was the first example of an immunomodulator binding to a neural system.

Other recombinant systems were under investigation including human growth hormone (pilot production), Interferon alpha and gamma (market end 1996) and Streptokinase (pilot production). The structure and function of insulin, arrowhead protease inhibitors A and B, human brain-derived neurotrophic factor (hBDNF), coagulation factor VIII, scorpion toxins, and thrombopoietin are also under investigation.

Developments in therapeutic proteins are being exploited through a new company, Shanghai Hua-Xin High Biotechnology Inc. The enterprise was founded by Professor Liu and is a joint venture between Shanghai Institute of Biochemistry, Shanghai Hua-Lin Pharmaceuticals Co., Hong Kong Hu-Kang Pharmaceuticals Ltd and Shanghai Biotechnology Research Centre. The company is involved in the R&D and manufacture of medically important drugs and reagents and is

listed as one of the top 20 enterprises in Shanghai. The company's main products, recombinant IL-2 and Interferon α_{2b}, are produced in a GMP facility, currently located in Shanghai, but shortly to be relocated to Pudong. With strong support from Shanghai Municipality, Hua Xin Inc. is investing 120 million RMB to expand the company at the Shanghai Biotechnology Industrial Park located in the Jinqiao area of Pudong new region. The new facility will include modern GMP manufactoring, advanced research laboratory and quality control laboratory in order to keep up with international standards.

Chinese Academy of Sciences: Institute of Cell Biology

The CAS Institute of Cell Biology was established in 1950 and currently has 66 scientists/engineers out of a total of 371 staff. The Institute has four departments: Developmental Biology, Oncology, Immunology and Molecular Biology. It also has several affiliated laboratories including the Max Planck Guest Laboratory, which receives 100,000DM per annum, the Shanghai Joint Laboratory of Life Sciences (CAS), the World Laboratory, the Blood Serum Laboratory, funded by the French, and one of a World-wide Network of Centres of Contraception, funded by the Rockefeller Foundation.

Scientifically, the main thrust of the Institute is to study life activities such as cell growth, differentiation, heredity, neoplastic transformation and the immune response, as well as their regulation and control, and to find new ways to solve practical problems in biotechnology, medicine and agriculture. The major research projects within the Institute include: artificial chromosomes as vectors, cell growth factors and receptors relevant to the control of cancer cell growth, monoclonal antibodies against human liver carcinoma and lung cancer, genetic engineering of human growth hormone, recombinant β-human chorionic gonadotropin as an infertility vaccine, protein engineering of tricosanthin, sperm membrane protein and immunology, *in vitro* maturation and fertilisation of the oocyte and individual gene expression in higher animals.

The activities in the group in the Laboratory of Cell Engineering fell within the general area of tumour immunology, monoclonal antibodies and diagnosis/therapy. A 27kDa protein tricosanthin is being investigated for value for mid-term abortion by its action on trophoblasts. The primary sequence and crystallographic structure is known plus some details on its immunological role in IgE-induced anaphyllactic shock. Joint studies with the Institute of Biophysics in Beijing on the protein engineering and modelling of the tricosantin have been identified and cDNA cloning and variable region sequence analysis of 5 mouse IgE monoclonals determined. There is some speculation that the protein may be used to treat AIDS, although no evidence for this proposal was presented.

Ongoing studies on lipopolysaccharide-induced macrophage function in order to kill cancer cells were described. Work on single chain Fv, chimaeric and humanised monoclonal antibodies using a phase-display antibody library was presented.

Several projects in tumour immunology were described. Several monoclonal antibodies to a hepatoma had been raised of which one is very specific for the tumour. When labelled with ^{131}I, the antibody regresses the tumour with a 31% survival rate after 5 years. Attempts to produce a similar monoclonal antibody against human lung cancer have proven more problematic. The group also have monoclonal antibodies against an ovarian tumour and are currently using these to develop ELISA diagnostics.

Chinese Academy of Sciences: Shanghai Research Centre of Biotechnology

This relatively new facility was established in 1989 with the aim of acting as a intermediary between Institutes of the CAS engaged in basic research and the more commercial world. The Centre employs 250 staff and has pilot plant facilities (15,100, 1000L fermenters) for up-scaling some of the developments taking place elsewhere. Major projects involved hGH, IL3, vaccines, insulin and TNFα. For example, IL3 was expressed in a 15L *E. coli* fermentation as an inclusion body, which when extracted in urea/guanidine hydrochloride and refolding gave active IL3. Chromatography on conventional ion exchange and gel filtration media gave grams of IL3 in a 20% overall yield. Tissue Necrosis Factor (TNFα) was isolated from cell free extracts by fractionation with ammonium sulphate, ion exchange and gel permeation chromatography to yield 10g > 95% pure TNFα from a 10L fermentation. The

centre supplements this more process-oriented work by research on 'biochemical engineering' and involving the formation of inclusion bodies, refolding, ultrafiltration and chromatography.

The Centre is a contract research organisation which concentrates on downstream processing, scale-up and optimisation but has no cGMP facility within the Centre. A brief tour of the laboratories revealed that the whole building was in poor shape, with inferior equipment, minimal facilities and little apparent scientific activity. Considering the building was newly constructed, it was a surprise to see so much neglect at what was promised to be such an important capability for the Shanghai area. However, one suspects that the concept of a Biotechnology Centre has been overtaken by events in the private sector and Pudong. Nevertheless, the CAS Research Centre for Biotechnology is one of the few centres in China which appear to specialise in downstream processing.

BEIJING AGRICULTURAL UNIVERSITY

Agrobiotechnology Laboratory

Molecular plant biology is concerned with viral diseases transmitted by fungi. One approach is to make plants resistant to the fungal vector (not the virus itself).

Infections in sugar beet appear to be a greater problem in China than elsewhere, giving rise to up to 70% losses per year. The fungus is very difficult to kill, and also to culture. A small test trial has been carried out for the last three years (three generations) sponsored by the Ministry of Light Industry.

Investigations are ongoing with wheat mosaic virus, transmitted by polymycytes and cucumber mosaic virus.

Post-harvest physiology of fruits and vegetables is a further main area of research. With tomatoes and kiwi fruit there are 30% post-harvest losses in tomatoes. The approach is to insert antisense to inhibit synthesis of athylene, a plant hormone which promotes senescence and ripening. Funding comes from the Ministry of Agriculture and Natural Science Foundation. The project is being exploited via a university-based company and has been passed on to a government seed company. The laboratory has worked in conjunction with the researchers responsible for the approach adopted by Calgene to delay ripening. The Chinese approach blocks athylene synthesis at different points in the pathway from that employed by Calgene.

Maize biotechnology aims to induce resistance to Maize Dwarf Mosaic Virus and to European Corn Borer and to investigate mutations responsible for male sterility.

Techniques for introduction of DNA into cells include microprojectile bombardment, ultrasonication and microinjection into ovary of maize.

Nitrogen fixation studies include research to overcome repression of nitrogen fixation by high concentrations of ammonia and plant hormones (giberellin), insecticides and bioplastics (pHB).

Plant genetic engineering is aimed at quality improvement in the amino acid balance in maize by taking sulphur-rich protein from rice and lysine-rich protein gene from potato pollen and use agrobacterium for transformation to transfer to maize.

The animal side is less well developed but animal physiological studies include maturation regulation of oocytes. The quality of the oocyte affects the success of creation of transgenic animals. A factor has been isolated which influences CAMP levels (via CAMP reductase). The factor is a steroid based lipid which is not species specific.

Transgenic animals work employs a new technique using a sperm as a vector for foreign genetic material (not involving micro-injection). The technique has the advantage of producing many animals in a short period of time. This has generated new intellectual property which is soon to be patented. Collaboration is taking place with Hubie provincial college of agriculture.

Workers have transfected pigs with porcine growth hormone coupled with ovine growth promoter. No joint defects have been observed, as have been seen in similar experiments in West.

Specific expression of foreign protein has been achieved in 80 transgenic sheep (expressed in mammary gland tissue) resulting in 0.5g/l

human growth hormone in milk. Also there is work with antitrypsin gene from Genzyme.

Sources of funding for Biotechnology in the Institute come from the 863 project Key Attack programme (5 years) which provides 50% of funding of biotechnology within the college and Natural Science Foundation - provides the other 50% of funding. This comes direct from the State Council.

BILONG INSTITUTE FOR TRANSGENIC ANIMALS IN BEIJING

The Bilong Institute for Transgenic Animals in Beijing was founded in 1994. It is a development institute whose staff are young scientists with M.Sc. and Ph.D degrees. Now, the research programmes of Bilong are focused on the following subjects: (1) To use transgenic animals and plants as bioreactors to produce biological active substances which have commercial value; (2) To establish transgenic animal models for diseases; (3) To develop transgenic animals and plants which can be commercialised.

One of the institute's main projects involves the breeding of mice with cataracts in an attempt to find a cure for this disease. The institute is also involved in research with some of the nation's top hospitals, and undertakes the development of transgenic animals for these and other institutions, drawing upon expertise from many fields.

This Institute is a recent development and is run by a group of young enthusiastic local scientists. It is not associated with the Chinese Academy of Sciences. The aim is to commercialise transgenesis and transgenic animals.

The Institute also intends to develop transgenic animals to protect rare species. For example tiger bone, antelope horn and rhinoceros horn are rare traditional Chinese medicines but the species from which they are derived are also rare. Transfer of genes to normal domestic animals may help safeguard these rare species!

The Institute intends to hold the first International Conference on Transgenic Animals in Beijing in November 1996.

CHINESE ACADEMY OF AGRICULTURE - BIOTECHNOLOGY RESEARCH CENTRE

The main function of this Institute, which was founded by the Ministry of Agriculture in 1986 is to conduct basic and applied research using cell and tissue culture, genetic transformation and recombinant DNA technology. There are 94 staff of whom 16 are senior scientists. The main areas of research are:

(i) Plant resistance to disease

(ii) Molecular basis of pest resistance

(iii) Nutrition improvement

About 50% of the cotton crop is lost annually to the Boll Weevil beetle, which costs about $750 million in lost revenues. They have artificially synthesised an insecticidal gene of *Bacillus thuringiensis* (B.t.gene) and introduced it into cotton (also tobacco). The transgenic plants show strong insecticidal activity. The mortality of insects which feed on it approaches 80%. Field trials will commence with this years crop. They have also cloned a proteinase inhibitor.

The second project is on protecting the potato crop, which is of serious concern in Southern China where temperatures and humidity are high. An antibacterial peptide gene has been synthesised and introduced into the potato. More that 200 transgenic lines have been tested, some of which have shown high bacterial resistance, which correlated quantitatively with the expression level of the peptide, which has only 37 amino acid residues. Crop protection is a high priority area of research in China, with a population of 1.2 billion (25% of the world's population), with only 7- 8% of the world's cultivable land.

The third project concerned nutritional improvement of crops. Agronomically important crops such as rice, wheat, potato, cucumber, melon, watermelon etc, which are high in protein (and unsaturated fatty acids) are important food sources for both humans and animals. Unfortunately, however, the levels of sulphur containing amino acids are too low to reach the nutritional requirement. A gene from rice has been introduced into alfalfa, and transgenic plants have been produced where levels of sulphur containing

amino acids have been increased by 7-10%, which improves sheep wool production when fed to sheep. This work is still experimental. The advantage of this approach is not clear, since sulphur containing amino acids are readily and cheaply produced synthetically and simply can be added to the feed.

Further studies aim to produce transgenic potatoes, tobacco, peppers and tomatoes which are resistant to viruses. This has been achieved by introducing a gene from a monoclonal antibody.

A major concern in the West regarding transgenic species is that of safety, and controls and procedures have been set up to address the issues. One gets the impression that there are very few controls in China and enforcement is poor.

Claims have been made for the development of a diagnostic (Mc Ab) test kit for testing of disease in plant seeds. They have developed a vaccine for IBD (poultry) and 7-8 others for various diseases and have produced 100 million doses (treats 700 million chickens) under CGMP. In general, however, their definition of CGMP falls somewhat short of Western standards. It is expected that a recombinant vaccine for poultry disease will be available within 3-5 years.

Funding is derived from various sources such as the National Science Foundation (70%), High Technology Research (863) programme, National Biotechnology Award, Ministry of Agriculture and International funding (Sweden).

The laboratory is 5200m^2 in size, together with 600m^2 of green houses. There is a lot of scientific equipment, including a DNA synthesiser, DNA sequencer, ultracentrifuge, ultra-low refrigerator, CO_2 incubator, plant growth chambers etc. Much of it appeared under utilised.

KEHAI MEDICAL BIOTECHNOLOGY CORPORATION

The Kehai Medical Biotechnology Corporation was established 13 years ago, jointly by the Municipal Government of Beijing and Chinese Academy of Science. There are over 900 employees, 15% of whom are professors/researchers. They are actively seeking international co-operation.

The Biotechnology Section has only been going for 3 years. They have also been working on computer science and chemistry.

Three areas of research were described as:

- Diagnosis of various diseases using PCR kits, especially pathological micro-organisms.
- Test kits for Hepatitis C, Herpes, HIV and Rubella infections (which are said to be about one year away from commercialisation).
- Human molecular biology, especially cancer metastasis. Unfortunately most of the published material was in Chinese, but we managed to extract the following information. They claim to have obtained a gene from tumour cells which does not occur in normal or non-metastatic cancer cells. It has 2.5 kilobase pairs. They are trying to construct an antisense gene to prevent metastasis as follows:

Using two rounds of classical and one round of pcr-based differential screening of a high metastatic cell (pGbt$_1$) cDNA library, 8 clones were obtained, named as pgc1 to pgc8. Northern hybridization confirmed that clone pgc1, pgc3, pgc6 and pgc7 were expressed at a higher level in high metastatic cells than in low metastatic cells. These 4 clones were sequenced and compared with the other genes in the Genebank. Clone pgc1, 411bp long, was unique showing no homology to any other genes in the Genebank. The actual size of its mDNA was about 2.1kb in length. Clone pgc3 and pgc7 shared >90% homology with two mitochondrial genes functioning along the metabolic pathway to produce energy and this is consistent with the properties of high metabolic states of metastatic cells. Clone pgc6 share homology with the enolase gene, another sugar metabolic gene.

Further investigation plans with respect to the various clones include:

Clone pgc: 1

Clone and characterise the full length of the cDNA sequence, predict the amino acid sequence and its biological function.
Determine the exact relation of this gene to the cancer matastatis.

Investigate the possibility of utilising this gene to prevent cancer matastatis according to the above results. Investigate other aspects of the gene itself, such as gene structure, chromosomal localisation etc.

clones pgc3, pgc6 and pgc7:

Determine the exact relations of these three genes to the cancer metastais.
Study one of the gene structure differences between in high metastatic cells and normal cells.

Develop specific substrate for the gene product of metastatic cells to inhibit the activities of these proteins. As these genes are involved in the energy metabolism, the inhibition of their activities may result in cell death.

On commercialisation of their work, they stated that they have signed agreements for each individual project, 50% of the shares belong to the Academy, 50% to local government.

MINISTRY OF HEALTH: DIVISION OF BIOLOGICAL PRODUCTS OF THE BUREAU OF DRUG ADMINISTRATION AND POLICY

Biotechnology is a high priority for the government and is a fast growing sector of the Bureau of Drug Administration, due to the large government investment and increasing speed of research in this area.

Areas of foremost interest are the recombinant Hepatitis B virus vaccines. The Merck Sharp and Dome licensed product yeast recombinant HepB sAg Hepatitis B vaccine appeared to be a government approved product that is produced and sold in China. The capacity for recombinant HepB vaccine production was claimed to be 20-30 million doses and the market up to 120 million doses a year but only 5 to 10 million are currently produced and sold. Another method of producing a Hep B vaccine, namely a vaccine virus based vector for presentation of Hep B antigens that is produced in CHO cells, was stated to be already marketed. We found no collaborating evidence supporting the marketing of this vaccine, however there were often misunderstandings as to whether a product was in clinical trials or on the market and what that difference means in China compared with the United Kingdom (see below).

The list of recombinant products currently considered by the department and their claimed status included: Erythropoietin (EPO, clinical trials phase II); Interleukin-2 (IL-2 marketed for treatment of kidney tumours with metastases and in phase IV clinical trials see below for an explanation); Interleukin-3 (IL-3, research); Granulocyte Colony Stimulating Factor (G-CSF); Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF); Nerve Growth Factor (NGF); Epidermal Growth Factor (EGF, marketed for treatment of burns but other groups suggested this is still in clinical evaluation); Streptokinase (SK, marketed). Also mentioned was a recombinant insulin as a future product as well as gene therapy Haemophilia B(factor) IX replacement. In addition, the native protein products for Factor VIII and Human Serum Albumin (HSA) derived from plasma (extracted at collection points) are controlled by the department. HSA is a major import product. As blood is bought rather than donated in China and it was difficult to obtain sufficient quantities of the required blood factors. The government was interested in moving away from imports and, for example, would not be interested in foreign made vaccines due to their costs.

The exact procedures in place for the testing and approval of recombinant products were difficult to determine. Research, development, testing, certifying and marketing of recombinant medicines are currently all essentially funded by the government. The State Science and Technology Commission (SSTC) funds new drug research at Universities and Technical Institutes. It appears that the clinical trials are funded and carried our by the government (through the Ministry of Public Health) and that the medicines are then certified by the Ministry of Health for sale (distribution). Factories in each of the six administrative zones of the country are identified to manufacture and distribute the medicines. In the past all of this was centrally controlled, funded and orchestrated. The opening to the West has introduced problems in this scheme that probably account for the difficulty in determining exactly at what stage each of the products are. It appeared that marketing and late phase clinical trials were most probably identical for the government. Since the government funds and controls both trials and distribution, distributing the medicine and recording the effects can be seen as both clinical trials and marketing.

The situation is changing as private companies increase and there will be a need for the government to alter its apparently closed door approach to biotechnology-derived medicines.

The distinction between those doing the research and development versus those regulating and certifying new medicines will have to become much greater. Moreover, rules governing the conduct of the two separate parties will need to be generated and these rules will require a good deal of definition and clarification.

THE CHINESE ACADEMY OF MEDICAL SCIENCES AND PEKING UNION MEDICAL COLLEGE

After a very warm welcome by a large delegation, it was explained that the Chinese Academy of Medical Sciences could be compared to the United States National Institutes of Health (NIH). The 19 Institutes, constitute, most in the Beijing area, the Academy. Total staff of the Academy is about 12,000 with 800 at the professor level and another 900 at the associate professor level. The institutes cover a wide range of topics. These include Medicinal Plants, Blood Diseases, Radiation Medicine. In particular the Institute of Pharmacy founded in 1958 has generated 250 new drugs and 170 patents. The Institute of Medicinal Biotechnology has developed 96 new antibiotics.

The biotechnology projects currently carried out by the Institutes of the Academy include EGF peptides for burns, calcitonin for osteoporosis and GM-CSF for replacement of white cells following radio/chemotherapy all of which are in clinical trials. In addition research is carried out on G-CSF, IL-4, IL-6, ANF, IL-2 hybrid with *Pseudomonas* toxin. In the area of antibiotics, derivatives of Kanamycin and Sperimycin are being tested to increase the expression levels of these antibiotics by the organisms that produce them.

There are 12 gene therapy projects and 20 protocols carried out under the CAMS. These include Factor IX replacement for Haemophilia B and introduction of the TK gene and treatment with gancyclovir for brain cancers. Three protocols dealing with liver cancers using IL-2 and MHC determinants to induce immune rejection of the tumour were mentioned. A cytosine deaminase protocol for immuno-deficient children, an Adeno E1a expression protocol to inhibit cERB-b2 in ovarian cancer, five protocols to treat pancreatic carcinomas by anti-sense to K- ras and EGF-R, plus protocols to introduce c-myc, and HSV-TK were listed. For oesophageal cancer a new anti-oncogene was claimed but not described, while for cervical carcinomas, HPV E6 and E7 were the targets. We also heard evidence of the virus HPV 16 is found in 18.6% of Chinese cervical cancer cases and therefore a target. Other approaches to treating this cancer are the introduction of TGFβ to introduce apoptosis in the tumour. Vaccines using the HPV16 late genes L1 produce in a Baculovirus system are being tested. Hypercholesterolemia was being attacked by an Adenovirus delivered LDL receptor; β-Thalesemia by β globin and activated γ globin; thrombosis by prourokinase, cancers in general by adding MDR to bone marrow to protect against chemotherapy and a proactive introduction of GST to prevent cancers.

At the National Laboratory of Medical Molecular Biology (founded in 1992) there is an emphasis on studying structure function relationships of medically important proteins. Regulation of the β globin and IL-2R genes are being studied using transgenic mice to investigate the tissue specificity of their enhancers. Other topics included the role of CD3 in apoptosis; renin gene expression in transgenic mice to study hypertension as well as generating an RDG hybrid ANF peptide expressed in *E. coli.* Another topic of investigation is the membrane proteins of sperm with an interest in making antibodies that will act as male contraceptives (so far seven new cDNAs have been identified). Work on monoclonal antibodies includes new differentiation markers for leukocytes, B lymphocytes in particular. Two new cDNA's have been isolated one of which encodes an unknown protein expressed on activated B-cells while the other is an α mannosidase that is surface expressed.

The Medical Genetics Institute carries out cytogenetics and molecular genetics for research and diagnostics. For three common conditions (PKU, β-Thalesemis, and Muscular Dystrophy) they provide diagnostics. They are also studying the chromosomal localisation of a rare genetic disease known as Crie Du Chat (CDC) that is inherited through a locus on Chromosome 5 (this work is sponsored by Denmark).

Funding of the Institutes' biotechnology basic research work is largely from the Chinese National Science Foundation. Development of the results into products is funded by outside companies. For example a Japanese company is funding new antibiotic work, the German pharmaceutical company Bayer as well as the American group Upjohn are also funding CAMS work and GlaxoWellcome is funding the Chinese medicinal plant programme. In general the major contributor countries to the CAMS programmes are Japan and the USA (especially for epidemiology of cancers).

BEIJING BIOLOGICAL PRODUCTS INSTITUTE (NATIONAL VACCINE AND SERUM INSTITUTE)

This Institute, founded in 1919 at the Temple of Heaven, moved to the present location in 1958 and now covers 567,000sq metres. It has approximately 1,400 personnel of which 46% are technical graduates and 110 are senior research workers or senior engineers.

It was stated that more than 100 kinds of vaccines, sera and diagnostic reagents are produced by the Institute. Twenty million doses of Hepatitis-B vaccine per year are projected!

The Institute is famous historically for the discovery of the trachoma agent (Prof. Tang Feifan). Other important developments include the plasma derived Hepatitis B vaccine, trivalent oral polio virus vaccine, refined diphtheria toxoid. More recent developments have been rubella vaccine, herpes simplex vaccine, DNA recombinant Hepatitis B etc.

New potential developments include a recombinant vaccine for rabies.

A special feature of the Institute is the Sino-Danish Biomedical Postgraduate Training Centre, founded in 1982 and jointly funded by China and Denmark (Danida). The Centre is well-equipped and is intended to train advanced and intermediate scientific technical and administrative personnel by experts from China and abroad. In recent years instructors from DANIDA, WHO, UNICEF, World Bank, America and Europe have participated in training courses.

The participants are accommodated at the Centre and dormitory, dining and gymnastic facilities are available. Capacity is approximately 100.

Courses generally last 2 weeks and are held throughout the year. No courses were in progress at the time of the visit.

SHANGHAI SCIENCE AND TECHNOLOGY COMMISSION

The OSTEMS delegation were met by the director of the Biotechnology and Pharmaceutical Industry Office, Shanghai Municipality, the Deputy Director, the Senior Biotechnology Engineer and the Program Officer. Most commission members held other positions as well as one on this committee. The principal point of the committee is to encourage, advise and select for funding local biotechnology efforts (university or otherwise) so as to increase the activity within Shanghai in this area. As a measure of the importance of Biotechnology, we were told that the Mayor of Shanghai was himself the President of this commission.

General background briefing about Shanghai was given, its history and current situation. Some salient points are the 13.8 million inhabitants of a city only 150 years old. There are 47 universities and colleges of which 10 work on biotechnology. Of 100 independent institutions some 30 are involved in biotechnology or pharmacology. There are 506 hospitals in the area some of which conduct clinical trials for new medicines.

Shanghai is rich in highly qualified personnel and presents an overall favourable environment for collaborative biotechnological research.

Funding for the work is provided by the government, some 30 million RMB a year of which one third is for research and two thirds for production. 70% of the funding goes to pharmaceuticals and the remainder to agriculture. Forty large pharmaceutical companies were claimed to be in Shanghai with a total of 200 counting all pharmaceutical companies. In 1995 the government sponsored more than 1,000 technical visits abroad (many for biotechnology). The areas which the commission suggested need the most foreign input were: gene therapy, transgenic animals, regulations to insure safety and security, large scale mammalian cell culturing, and down stream processing.

A substantial list of recombinant proteins sponsored by the Commission was detailed and information was presented about new antibiotics and industrial enzymes. Some 30 micro-organisms are currently being cultured for their production of antibiotics. Fourth generation semi-synthetic antibiotics were claimed to be made as well as neutral and acid proteases, amino acid generating enzymes (10 different products) and immobilised enzymes.

Overseas funding is welcome and though this must be with a local partner there is no restriction on the share of the partnership.

FUDAN UNIVERSITY: INSTITUTE OF GENETICS

At this university, in the human genome laboratories, very detailed information was provided on gene therapy and human genetics.

Haemophilia B afflicts about 15,000 patients in China who currently must receive blood transfusions to reduce their tendency to bleed uncontrollably. Haemophilia B is due to an insufficiency in Factor IX. This disease is easier to treat by gene therapy than the more common Haemophilia A disease, because the gene given is much smaller than the Factor VIII gene for Haemophilia A. Over the last ten years, an animal model (in the rabbit) to test gene therapy protocols has been developed. Moreover an *ex vivo* technique with patients' fibroblasts infected with retrovirus carrying wild type Factor IX gene has been used to reintroduce the cells and production of the protein into patients. Four patients treated with this technique using expanded autologous fibroblasts in a glycogen matrix placed in their peritoneum have shown good responses and produced measurable Factor IX for about six months. After this the expression level falls off (possibly due to the death of the transformed cells in the matrix). Current studies are to improve the vector for safety and adding the first intron from the gene to increase expression of the protein. These steps are being tested in the rabbit model first before humans. The current limit to treating more patients is the ability to multiply up enough of the transformed autologous fibroblasts.

The Director of the Human Genome Laboratory in the Institute of Genetics informed us that the Institute has 150 staff and 100 graduate students and is considered one of, if not the, best genetics institute in China. Work is carried out on plants, micro-organisms, *Drosophila* and humans. For example a new Taq-like polymerase has been isolated form a micro-organism. He has worked on the generation of YACs from Chinese white blood cells and markers for the X chromosome. His group has also cloned the recently described gene for Duchene Muscular Dystrophy and examined the defect in 180 patients who mostly showed deletions in the gene. The group has also been studying the DMD promoter to determine how different cell type expression is regulated. His group is now participating in the analysis of diabetic patients (Type II) who have been collected over the last three years. This group of 153 pedigrees covers three generations in each case with three afflicted individuals. He indicated that Sequana, the California genomics company, had visited to discuss a possible collaboration but nothing had come of the talks. He also indicated most sequencing was manual due to the high costs of reagents for automated sequencing. In addition high costs of reagents meant only limited manual sequencing was possible, so that they concentrated on mapping genes not identifying them.

SHANGHAI NUMBER ONE MEDICAL UNIVERSITY

This medical school was the first Medical University run by the Chinese themselves. It currently has about 500 students in each year, 200 of whom are awarded masters and 100 are awarded doctorates.

The major interests in biotechnology are in the cardiovascular area where clotting and myocardial infarct are the most important aspects. Hence recombinant streptokinase, staphlokinase and tissue specific plasminogen activator (tPA) are principal interests. The two kinases are made in *E. coli* while they are using CHO cells grown on microcarriers to produce the tPA. Some clinical experience has been gained with each of these from small scale produced protein. Beginning in 1994 recombinant streptokinase was used to treat myocardial infarct. Compared with a native protein the recombinant protein shows equal efficacy among 122 patients treated up to date. GMP facilities existed and were used to produce the rSK on a small scale. About 840 grams a year can be produced and this is sufficient for 56,000 doses. This is not sufficient for the country, however, and more

foreign investment in production plants planned for the near future is needed to allow for greater production capacity.

SHANGHAI CANCER INSTITUTE

The major projects in this Institute are a human genome project relating to oncogenes especially in liver cancer, hepatitis B virus and its relationship to liver cancer and gene therapy. Breast and liver cancer were particularly prevalent in China and, therefore, a major target for this group. The role of the transthyretin (pre-albumin) gene in liver cancer is being studied. The protein is a tetramer of 147 amino acid subunits which is involved in thyroxin transport and is synthesised in the liver. Impressive work on gene therapy through the Bureau of Drug Administration in Beijing and other projects on genes relevant to apoptosis is in progress.

KEXING BIOLOGICAL PRODUCTS CORPORATION

This is a biopharmaceutical joint venture owned by Peking University's winning Biotech Group and H&Q Asia Pacific, a US investment forum. It was approved in 1989 and occupies a factory on Shenzhen Science and Industrial Park. It is the largest biopharmaceutical manufacturing plant in China. It concentrates on genetically engineered pharmaceutical products of which recombinant α-1b interferon was the first. Three million doses per year are planned to be produced.

SHENZHEN KANGTAI BIOLOGICAL PRODUCTS CO. LTD

Shenzhen Kangtai Biological Products Co., Ltd. (SKTB) is a high-tech enterprise which integrates R&D, production and marketing of biotechnology products. SKTB is one of the assigned enterprises by the Ministry of Public Health to manufacture epidemic prevention products. SKTB undertakes one key technology import project of the Ministry of Public Health, the importation of recombitant Hepatitis B vaccine process know-how from Merck & Co., Inc. In June, 1994, the manufacturing facility of this project began successful production with an annual production capacity of 20 million doses of recombinant Hepatitis B vaccine. SKTB invested 170 millions RMB on this project. Now SKTB has cGMP facilities and advanced production technology of the 1990's. SKTB implement Merck manufacturing and quality standards and the products meet Merck requirements.

XINGPENG BIOLOGICAL PRODUCTS CORPORATION

This corporation occupies new buildings adjacent to other biotechnology companies in the Shenzhen Science and Industry Park. The park is some 20 kilometres from Shenzhen, a city which reputedly has mushroomed from being a small fishing village of some 300 inhabitants to 3 million in 10 years.

Hong Kong is a short distance away (40 minutes by ferry) and it is clear it is having a decided influence on the culture and finance of Shenzhen.

The mission of this corporation is to develop new biotechnological products, then to sell them to production companies such as Kexing Bioproducts Company. Kexing was in fact sponsored by Xingpeng and Kexing products are largely those developed by Xingpeng.

As with other institutes Hepatitis B vaccine is a major focus for research. Other products under investigation or development include interleukins (IL-2, IL-3) enythropoetin and interferons.

Useful relationships exist with overseas companies (e.g. Pharmacia) who provide training and capital equipment.

Appendix III

Order of the State Science and Technology Commission of the People's Republic of China

No. 17

Safety Administration Regulation on Genetic Engineering is hereby Published and Enforced.

SONG JIAN
Chairman
State Science and Technology
Commission of China
December 24, 1993

Chapter One: Safety Administration Regulation on Genetic Engineering

1. This regulation is aimed at promoting research and development of biotechnology in China, tightening safety control of genetic engineering work, guaranteeing public health of common citizens and genetic engineering workers, preventing environmental pollution, and maintaining ecological balance.

2. The genetic engineering items covered in this regulation include recombinant DNA technology using the vector system, and direct introduction of heterologous DNA into organisms by using physical or chemical means. The following genetic manipulations are not included.

   (i) Cell fusion technology and protoplast fusion technology

   (ii) Traditional hybridization and propagation technology

   (iii) Variation induction technology, in vitro fertilisation technology, cell or embryo culture technology

3. The regulation is applicable to all genetic engineering work underway in the territory of the People's Republic of China, including experiments, pilot tests, industrial production, release of genetic engineered organisms and utilisation of finished genetic engineering products.

   The genetic engineered organisms imported from outside China when being adopted in genetic engineering work in China, should abide by this regulation.

4. The State Science and Technology Commission is responsible for the nation-wide genetic engineering safety work. A national genetic engineering safety committee has been set up to handle safety supervision and coordination.

   Relevant administrative departments under China's State Council carry out safety administration of genetic engineering work according to the related regulations within their own responsibility scopes.

5. Safety administration of genetic engineering work is carried out on the basis of safety class control and classification approval, which means that different categories of genetic engineering work should be approved by relevant administrative departments.

Chapter Two: Safety Classes and Safety Evaluation

6. According to potential risk levels, genetic engineering work is divided into four safety classes:

   Safety class I:
      genetic engineering work of this class has no threat to human health and ecological environment
   Safety class II:
      genetic engineering of this class has low-level risk to human health and ecological environment
   Safety class III:
      genetic engineering work of this class has intermediate-level risk to human health and ecological environment
   Safety class IV:
      genetic engineering work of this class has high-level risk to human health and ecological environment

7. The technical and environmental standards of different safety classes for different categories of genetic engineering work are formulated by relevant administrative departments of the State Council of China, and then submitted to the national genetic engineering safety committee for record.

8. Institutions carrying out genetic engineering work should conduct safety evaluation to assess potential risk, determine safety class and work out corresponding safety control methods and measures.

9. Institutions carrying out genetic experimental research should conduct evaluation on DNA donors, vectors, hosts and genetic engineered organisms. The evaluation should be focused on the pathogenicity, carcinogenicity, chemical resistance, transfer possibility, and the effects on environment of target genes, vectors, hosts and genetic engineered organisms, and on determining biological control and physical control classes.

10. Institutions carrying out genetic engineering pilot experiments or industrial production should conduct safety evaluation on the physical barriers of the equipment and facilities of the culture, fermentation, separation and purification processes according to genetic engineered organisms safety class, to determine the safety class of pilot experiments or industrial production.

11. Institutions carrying out the release of genetic engineered organisms should conduct evaluation on the safety of genetic engineered organisms, the purpose of the release, ecological environment conditions of the release site, releasing safety methods, monitoring means and control measures, to determine the safety class of the release.

12. Biological tests should be conducted on finished genetic engineering products for safety evaluation, which will determine the possible impact of genetic engineering products on the public health and ecological environment.

Chapter Three: Application and Approval

13. Institutions carrying out genetic engineering work should submit applications to relevant administrative departments at different levels according to genetic engineering products' utilization scope and safety class before being approved to kick off.

14. Institutions carrying out safety class I and safety class II genetic engineering experiment research should get approval from the heads of their institution's administration. The work of safety class III should be examined by chief administrators of the institutions and then be submitted to relevant departments under the State Council for approval. The work of safety class IV should be examined by relevant State Council departments and then be submitted to the national genetic engineering safety committee for approval.

15. Genetic engineering pilot experiments of safety class I should get approval from chief administrators at the institutional level. The work of safety class II should be approved by responsible State Council departments. The work in safety class III should be approved by relevant State Council departments and be submitted to the national genetic engineering safety committee for record. The work in safety

class IV should be examined by relevant State Council departments and submitted to the national genetic engineering safety committee for approval.

16. Genetic engineering industrial production, release of genetic engineered organisms and utilization of genetic engineering products, if in safety class I to III scope, should be approved by relevant administrative departments under the State Council and submitted to the national genetic engineering safety committee for record. The work in safety class IV should be examined by relevant administrative departments of the State Council and submitted to the national genetic engineering safety committee for approval.

17. Institutions carrying out genetic engineering work should go through the following application procedures:

    (i) The chief of the planned genetic engineering project should evaluate the safety of the project and fill in the application form

    (ii) The academic committee of the institution should conduct technical evaluation on the application

    (iii) Application should be submitted along with technical documents

18. All genetic engineering work meeting the following requirements should be given approval and certificates issued at the same time.

    (i) No doubt has been found on the safety evaluation of the project applied.
    (ii) No threat to the public health and ecological environment has been found if the genetic engineering project applied has adopted safety control measures which are up to modern scientific and technological standards, according to the requirement of its safety class.

    (iii) The project chief and staff members are qualified for conducting genetic engineering work and have acquired necessary professional knowledge and safety operation knowledge. They have no hesitation in carrying out the obligations specified in this regulation.

    (iv) The project accords with relevant state regulations and laws.

Chapter Four: Safety Control Measures

19. Institutions carrying out genetic engineering work should formulate safety control measures and work out safety operation regulations in accordance with safety class.

20. Institutions carrying out genetic engineering work should work out relevant safety measures to handle waste materials according to the safety class. The remaining genetic engineered organisms should be killed before discharge to prevent spread and environment pollution.

    Institutions carrying out genetic engineering work should formulate measures to prevent emergency accidents. The measures should be listed as part of safety operation regulations.

21. Genetic engineered organisms should be stored in specific containers. The storage site should have its physical control fit in with their safety class. The storage of genetic engineered organisms of safety class IV should be supervised by specific person. Institutions carrying out genetic engineering work should compile a list of storage catalogues for inspection.

22. Transporting or transferring genetic engineered organisms should guarantee that specific containers used fit the safety class of the organisms. It should also be guaranteed that transportation or transfer strictly abide by relevant state laws and regulations on transporting or mailing of biological materials.

23. Institutions or individuals carrying out genetic engineering work should write down a detailed safety control record and keep the record for a period of no less than 10 years for inspection.

24. Institutions if causing harm to the public health or causing environment pollution due to carrying out genetic engineering work must take immediate measures to prevent the harm of the pollution from spreading and report to relevant administrative departments.

Chapter Five: Legal Responsibilities

25. In any of the following cases, relevant administrative departments will issue warnings, stop operation, suspend financial support, confiscate illegal profits according to actual conditions of violation.

    (i) The genetic engineering project begins operation without approval.

    (ii) Equipment, apparatus, laboratories which do not fit in with regulations have been used.

    (iii) Violation of safety operation regulations of genetic engineering work.

    (iv) Violation of other rules under this regulation.

26. The approval office staffs who has direct responsibility for neglecting duties, receiving bribes or practising irregularities will be punished with administrative disciplinary measures by the higher authorities.

27. The responsible unit of those violating this regulation and causing one of the following results must immediately stop the violation and take measures to handle the pollution and compensate for losses. In the event of a breach, those who are directly responsible will take criminal responsibility according to the laws.

    (i) Causing serious environment pollution.

    (ii) Causing damage or harm to the public health.

    (iii) Causing severe damage to ecological resources and ecological balance.

28. The staff in the approval office and specialists who are involved in the approval process are responsible for keeping the technical secrets for applicants.

Chapter Six: Supplementary Articles

29. The meaning of the special terms in this regulation

    (i) DNA, short for deoxyribonucleic acid, is the genetic material for storing genetic information of living things.

    (ii) Gene, is a functional and structural unit of genetic information which controls characteristic of living things. It is the DNA section with genetic information.

    (iii) Target gene is the heterologous DNA fragment for the modification of genetic constitution of host cells, and for the expression of genetic information of host cells.

    (iv) Vectors are the DNA molecules capable of transferring heterologous DNA into host cells and capable of self-duplication.

    (v) Host cells or receptor cells are those cells into which recombinant DNA molecules have been introduced.

    (vi) Recombinant DNA molecules are hybrid molecules which consist of heterologous DNA and vector DNA.

    (vii) Organisms refer to the living cells or living things which can propagate or can transfer genetic materials.

    (viii) Recombinants refer to the organisms into which the heterologous DNA have been introduced with natural factors or artificial means to change their genetic constitution.

    (ix) Variants refer to the organisms whose genetic materials are changed by natural factors or artificial factors.

    (x) Recombinant DNA technology refers to the technology which artificially modifies the genetic

constitution of the organisms with vector systems, e.g. the recombination of heterologous DNA and vector DNA with enzymes into a recombinant DNA molecule which is transferred into host cells to multiply heterologous DNA and express its function.

(xi) Genetic engineered organisms refer to the organisms coming from the genetic manipulation of genetic engineering, including genetic engineered animals, plants and micro-organisms.

The following variants and recombinants do not belong to genetic engineered organisms.
The living organisms coming from cell fusion and protoplast fusion.
The animals and plants coming from traditional hybridization technology.
The living things whose genetic constitution has been changed by physical and chemical inducing technology, and the living things which have teratogeny in their chromosome structure and number.

(xii) Genetic engineering products are products with genetic engineered organisms, its components or products coming from the expression of target gene in genetic engineered organisms.

(xiii) Genetic engineering experimental research refers to laboratory-scale research work on genetic engineering conducted within a control system.

(xiv) Genetic engineering pilot experiments refer to experiments or pilot production in a control system aimed at testification, supplementation of relevant data, determination and perfection of technical rules (product specifications and operation processing rules), to test the key technology for large scale production, before the application of genetic engineering experiment research results into industrial production (falling into production pattern and appraisal).

(xv) Genetic engineering industrial production refers to commercial production of drugs, agricultural chemicals, veterinary chemicals, fodders, fertilisers, food, additives, raw material of the chemical industry in the control system by using genetic engineered organisms. It also includes utilising genetic engineering in the technical processes of metallurgy, oil exploration and the recycling of waste materials.

(xvi) Release of genetic engineered organisms refers to research, production and application of genetic engineered organisms in an open system, including releasing genetic engineered organisms into natural ecological environments, such as cropland, grazing land, forests, mineral deposits and water areas etc.

(xvii) Utilisation of genetic engineering products refers to putting genetic engineering products into market for sales for utilisation by human beings.

(xviii) Control system refers to the operation system established through physical and biological controls.

Physical control refers to airtight sealing of the equipment, special installation design and safety operation which aim at reducing the spreading of potentially dangerous DNA donors, vectors and host cells or genetic engineered organisms to the environment to the lowest level.

Biological control means using genetic modification to reduce to the lowest level the abilities of vectors and host cells with potential risks to survive, propagate and transfer outside the control system.

Any operation system not fitting in with the above-mentioned control conditions is called an open system.

30. Relevant administrative departments of China's State Council should formulate their own detailed implementation measures according to this regulation within the scope of their responsibilities.

31. This regulation is explained by the State Science and Technology Commission of China.

32. This regulation is enforced from the date of publication.

Appendix IV

OSTEMS BIOTECHNOLOGY MISSION: 18-28 MARCH 1996
OUTLINE PROGRAMME

DATE	TIME	APPOINTMENT
Sun 17	10.45 am	Arrive Beijing by BA039
Mon 18	10.00 am	Embassy/British Council briefing (British Embassy Office) *Stephen Brown, Commercial Counsellor and Bhaskar Chakravati, First Secretary (Cultural)*
	2:00 pm	CNCBD (China National Centre for Biotechnology Development) & CUBC (China United Biotechnology Corp) *Ding Yong Deputy Director CNCBD*
Tue 19	10:30am & lunch	Beijing University: College of Life Sciences *Chen Zhanghong, Director* *Ding Mingxiao, Deputy Director*
	2:00pm	Qinghua University: Department of Biology Biotechnology *Zhao Nanming, Director*
	3:30pm	CAS Institute of Genetics *Chen Shouxi, Director*
Wed 20	10:00 am & lunch	Beijing Agricultural University Agrobiotechnology Lab *Chen Yongfu, Director* *Pan Chungang, Director*
	2:00pm	CAS Institute of Microbiology: *Meng Guangzhen, Director of CASIM, also Deputy Director of Biotech Dept, CAS*
	4:30pm	Bilong Institute of Transgenic Animals *Li Birong, Director*
Thur 21	9:00am	Chinese Academy of Agriculture Biotechnology Research Centre *Huang Dafang, Director*
	12:30pm	Lunch hosted by HMA at Residence

	3:30pm	Kehai Medical Bio-tech Corp *Chen Yubao, Director General*
Fri 22	9:00am	Ministry of Health *Dr Zhang Xilan, Deputy Director*
	3:00pm & dinner	CAMS (Chinese Academy of Medical Sciences) Beijing Union Medical University *Ba Denian, President* *Lu Shendong, Vice President*
Sat 23		No appointments
Sun 24		No appointments
Mon 25	9:00am	EU Delegation *Luc Vandebon, Counsellor (S&T)*
	1:30pm	Beijing Biological Products Institute *Zhao Kai, Director*
	7:05pm	Fly to Shanghai
	9:50pm	Arrive at Shanghai
Tue 26	9:00am	British Consulate General *Mr Simon Featherstone, Consul General* Shanghai
	10:30am	Shanghai Science & Technology Commission *Mr Li Minjun, Director Int'l Coop Office* *Government Building, Renmin Da Dao* Mr Wang Jiaoping, Deputy Director, Shanghai Biotechnology & Pharmaceutical Industry Office
	1.00 pm	Fudan University - Institute of Genetics (Human Genome Lab) *Dr Cai Jianhua* *Prof Xue Jianglun*
	3.30 pm	No 1 Medical University - Biotech Lab *Prof Song Heyan, Director*
	7:00pm	Dinner with Bill Marshack (US v Consul) for Lord Soulsby at Hilton

Wed 27	8:30am	CAS Institutes of Biochemistry *Prof Li, Director*
	10:00am	CAS Institute of Cell Biology *Prof Guo, Director*
	12:00pm	CAS Biotech Research Centre *Prof Yang Shenli, Director*
	3:00pm	Cancer Research Institute
	7:05pm	*Dr. Jian Gu* *Director*, National Laboratory for Oncogenes depart Shanghai for Shenzhen
	9:30pm	arrive at Shenzhen
Thur 28	9:30am	Kexing Biological Products Corp. *Dr. Kai T.Tam* *Vice President*
	11:30am	Kangtai Biological Products Corp. *Sheng Guangyang, Director/ Mr Doug Jian, Manager*
	2:30pm	Xingpeng Biological Products Corp. *Dr. Bi Zhigang, Director* *Peng Jinzhi, Vice General Manager*
Fri 29		Boat to Hong Kong
	11:30pm	depart Hong Kong for London

Appendix V

CONTACT LIST FROM

DOCUMENTATION PROVIDED BY INSTITUTIONS AND COMMISSIONS

HIGH TECHNOLOGY RESEARCH AND DEVELOPMENT
PROGRAMME OF CHINA
THE STATE SCIENCE AND TECHNOLOGY COMMISSION
(54 San - Li - He Road Beijing 100862. China)
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Fax (861) 2564095

PEKING UNIVERSITY-COLLEGE OF LIFE SCIENCES.1993
(Beijing, 100871, China)
Tel (861) 250 1840
Fax (861) 250 1844
The 70th Anniversary of the founding of the
Department of Biology, Peking University 1925-1995

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INSTITUTE OF MICROBIOLOGY
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Report of Key Laboratory of Crop Molecular and Cell Biology, Biotechnology
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